VOLUME 58 • AUGUST 1957 • NUMBER 2

A.M.A. ARCHIVES OF OPHTHALMOLOGY

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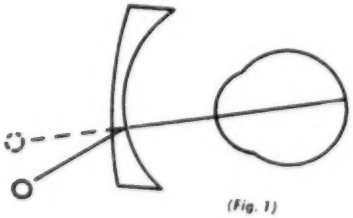

(Fig. 1)

This base down prism makes objects appear farther away and higher than they really are. See figure 1. The myope, before bifocals fixed his line of vision through a point 8 mm. below the distance center, invariably tipped his head and looked through a point near the distance center, thus avoiding prismatic effect. The hyperope on the other hand is not troubled by the base up prism he encounters and has little or no difficulty with bifocals.

From the foregoing it would seem that if the base prism found in the segments of myopic bifocals could be neutralized, the problem would be solved. We have found this to be true. We have also found that the only practical way to accomplish this neutralization is by "slabbing off" the proper amount from the bifocal segments. See figure 2.

(Fig. 2)

If we take a case requiring O.U.-6.00 with a + 2.00 add made up in a small segment bifocal, we would "slab off" 4.8 degrees of prism base up from both segments. (6×.8=4.8) that is, the distance correction through the 90th meridian times .8, the distance in cms. from distance center to reading point, equals the amount of base down prism that must be neutralized.

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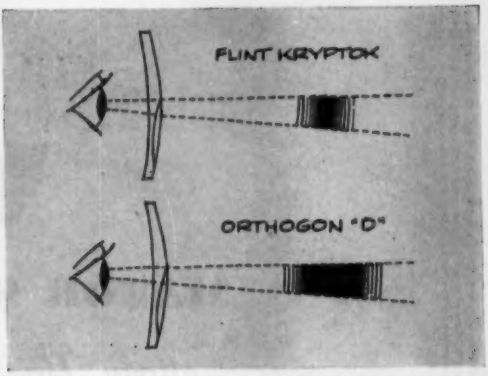

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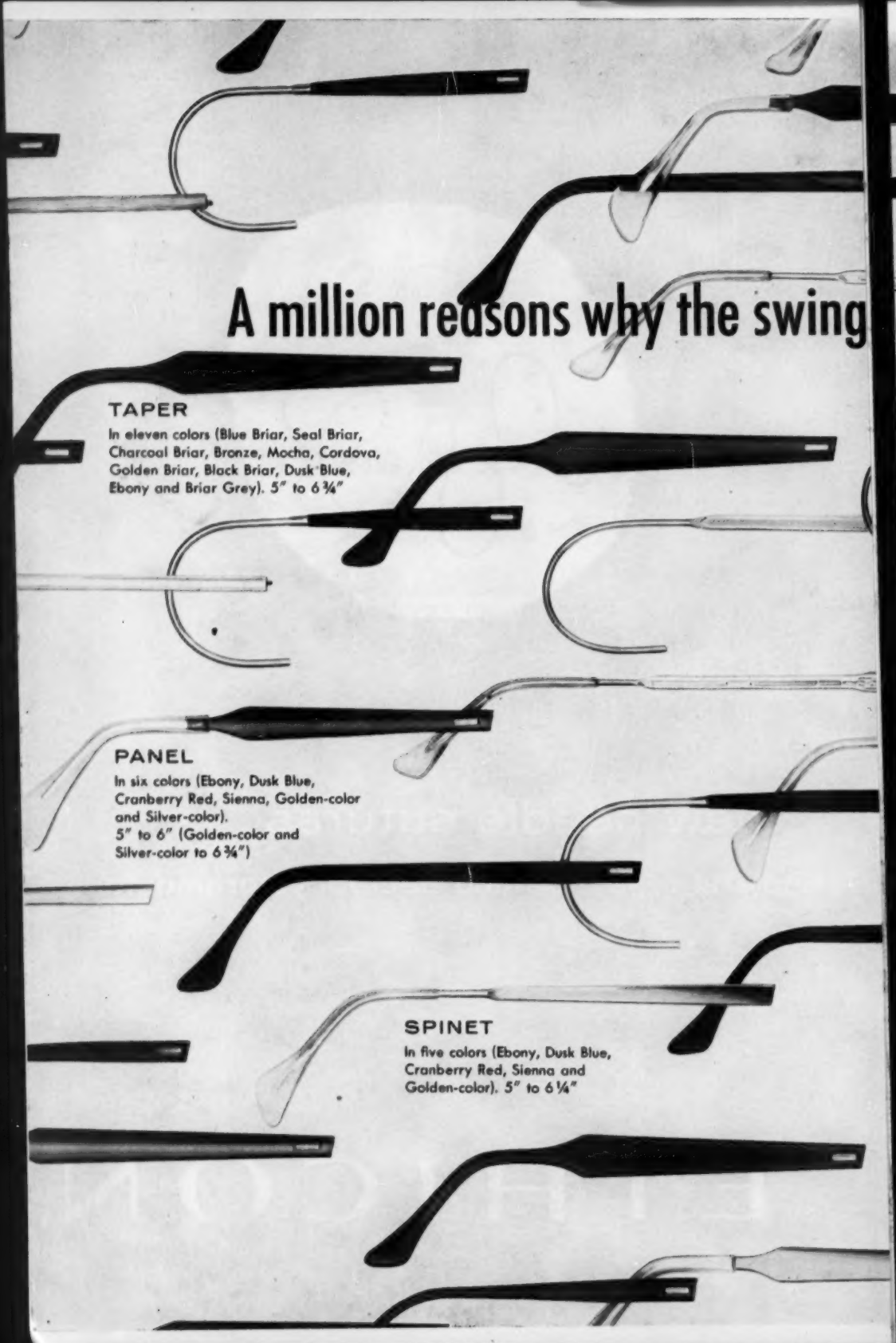
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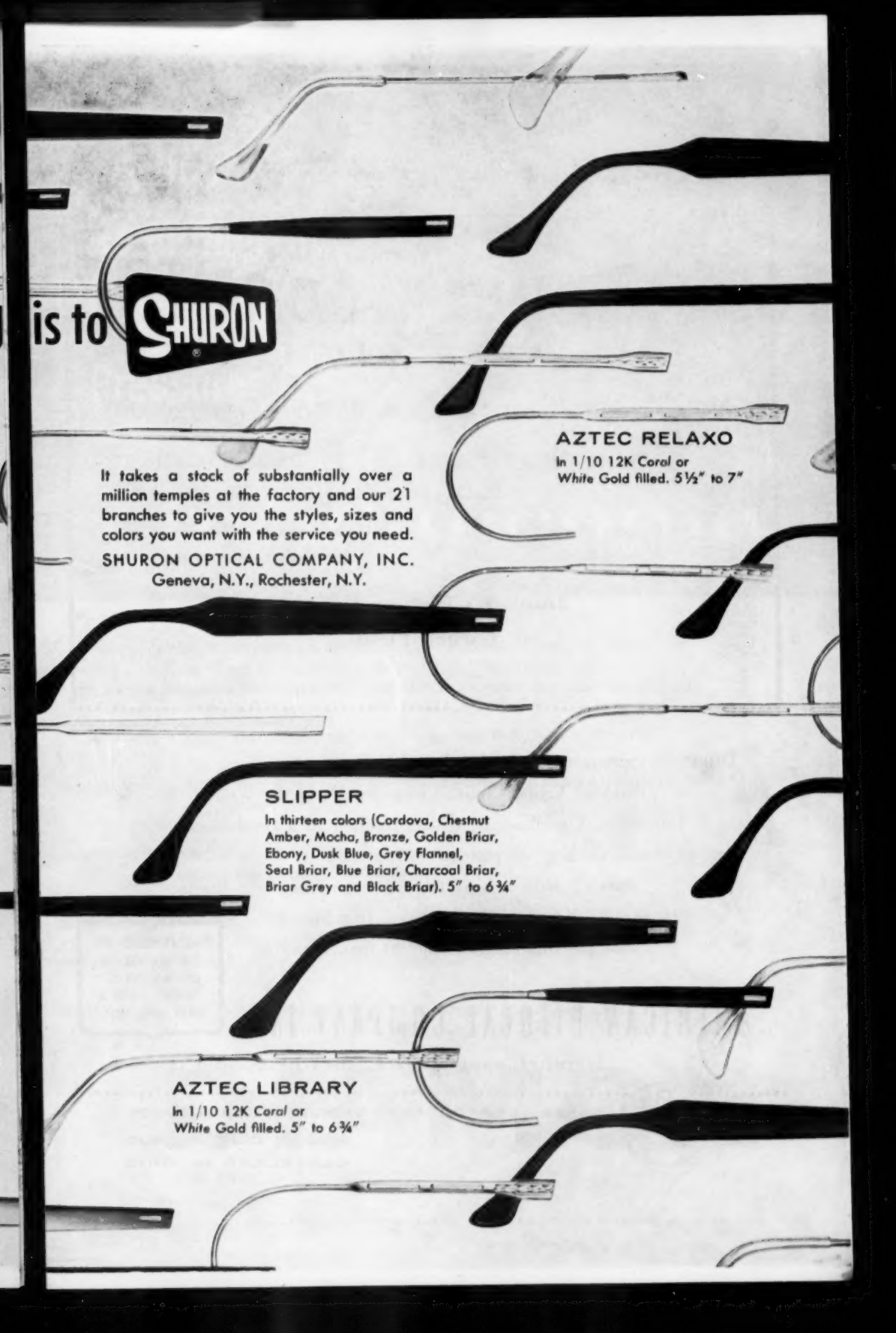

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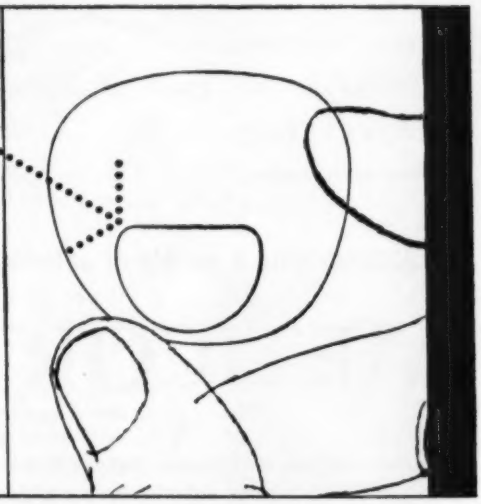

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JOHN J. KENNEDY, M.D., and CLYDE B. COPE, M.D., Fort Howard, Md.

Recurrent intraocular hemorrhage in young adults was first described by Eales, in 1880. He reported five cases in men between 14 and 29 years of age with recurrent hemorrhages in the retina adjacent to the veins and in the vitreous. He thought that constipation and epistaxis were etiological factors. Since that time, numerous causes have been suggested for this condition and have included calcium deficiency with diminished parathyroid secretion,[2] thromboangiitis obliterans,[3] septic foci,[4] and tuberculosis.[5]

In 1930 Cook[6] discussed a patient with subarachnoid hemorrhage and sickle-cell anemia in whom a retinal hemorrhage was also noted. In 1952, Edington and Sarkies[7] reported two patients with sickle-cell anemia and retinal microaneurysms; one of these patients had a vitreous hemorrhage. In the year 1950, Henderson[8] published 54 cases of sickle-cell anemia in which retinal hemorrhage was a presenting sign or symptom. In 1937, Harden[9] reported two Negro children with sickle-cell anemia in whom he described dilation of the retinal vessels with marked venous tortuosity. Henry and Chapman[10] examined 29 patients in 1954; 19 were classified as having a sickle-cell trait and 10 as having sickle-cell anemia. Although these authors mention doing electrophoretic studies of the hemoglobin in a few patients, they did not derive aid or draw conclusions from them. Such studies are invaluable in distinguishing sickle-cell anemia (S-S hemoglobin) from sickle-cell hemoglobin C disease. Henry and Chapman stated that they did not find systemic disease or foci of infection in nine patients with sickling and choroidal, retinal, or vitreous changes. They omitted mentioning whether two of the nine cases had either the trait or the anemia. These two patients had retinal hemorrhages in their left eyes. One also had several fluffy white patches in the temporal retina. Two others of the nine were said to have the trait. Of these two, one had a chorioretinal atrophy in one eye; the other had a filmy white mass following the course of the inferior temporal vein. Some of these ocular findings could be the result of any anemia, and others could be caused by an active or old chorioretinitis or periphlebitis. Of five patients with anemia reported by Henry and Chapman, two presented only chorioretinal atrophy; one had dilation and tortuosity of the retinal tree and retinitis proliferans, and two had vitreous hemorrhages and retinitis proliferans in common. One of the last two patients had retinal hemorrhages and white fibrous tissue covered by capillaries, and the other had chorioretinal atrophy besides those findings previously noted. In their extensive study of sickle-cell hemoglobin C disease, in 1953, Smith and Conley[11] reported three patients with intraocular hemorrhages. One of these also had aneurysmal

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dilatation of the vessels in the region of the macula.

Recently, Hannon [12] reviewed 140 cases of sickle-cell disease in which electrophoretic patterns had been made. Of these, 20 had sickle-cell hemoglobin C disease, and 7 of these had vitreous hemorrhages. He felt that vascular changes in the retina were likely to occur in the temporal quadrants. Two patients with sickle-cell hemoglobin C disease had twisted, corkscrew-like venules in the peripheral retina and some occlusion of the venules, with chorioretinal atrophy.

Sickle-cell disease refers to the pathological condition attributable to the homozygous or heterozygous sickle-cell state. In the homozygous state, the hemoglobin consists almost entirely of the sickle-cell type, combined usually with a small amount of fetal hemoglobin. This is symbolically represented as S-S hemoglobin and is synonymous with true sickle-cell anemia. In the heterozygous state, sickle-cell hemoglobin coexists with normal (A) or other abnormal (C, D, E, etc.) hemoglobin, and the condition is represented by the symbols S-A, S-C, S-D, S-E, etc., respectively.

hemolytic anemia with or without icterus, hemolytic crises, reticulocytosis, musculoskeletal complaints, hematuria, and hepatomegaly.[13,16] A large percentage of circulating target cells and splenomegaly, the latter tending to wax and wane during the clinical course of the disease, are almost constant features. With the exceptions of Smith and Conley and Hannon no one has commented on the intraocular lesions in hemoglobin S-C disease.

Sickle cells are rigid and cannot alter their shapes as normal red blood cells do, becoming impacted in the capillaries. This causes stasis, thrombosis, and hemorrhage.[17,18] The oxygen supply to the local blood vessels becomes diminished, producing an endarteritis and, finally, infarction of the involved area.[19,20]

Sickle-cell hemoglobin C disease, in which there is a combination of S and C hemoglobins, is clinically characterized by a mild

We have examined 20 patients in whom a diagnosis of sickle-cell disease was made

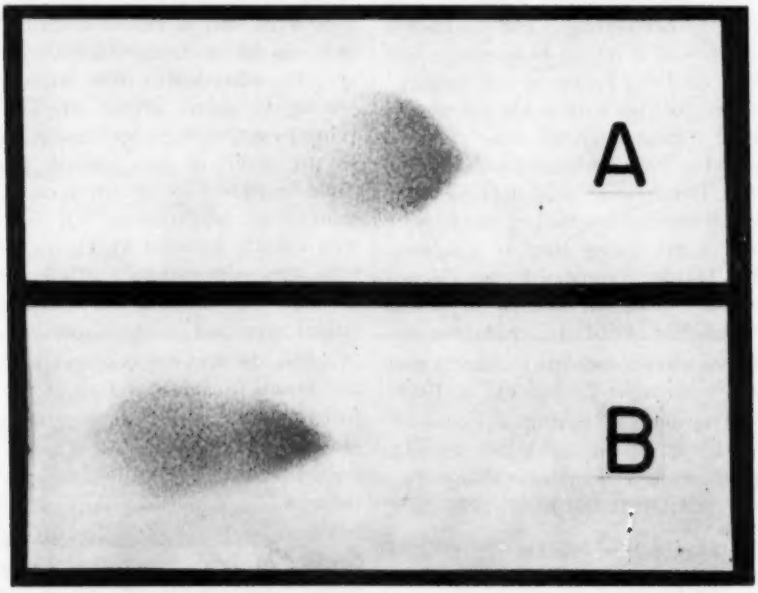

Fig. 1.—The partitioned hemoglobins of (*A*) normal adult control and (*B*) Case 1, who had the S and C components.

by conventional methods. The hemoglobin of each of these persons was resolved on paper by electrophoresis by use of a method previously described.[14] One patient had sickle-cell hemoglobin C disease; two had S-S hemoglobin (sickle-cell anemia), and the remaining seventeen had hemoglobin S-A.

Paper electrophoresis of the hemoglobin of Case 1 (see below) readily partitioned and effectively demonstrated the S and C components (Fig. 1). Studies of solubility of the hemoglobin were not performed, as they would have added very little to this study. There appears to be only one limitation of the electrophoretic method used in Case 1. At an alkaline pH, hemoglobins C and E have almost identical mobilities. This has been a source of confusion on at least one occasion in the literature.[21] Further identification at an acid pH in a Tiselius apparatus was not possible, but the singular rarity of hemoglobin E in the western hemisphere would tend to refute the possibility of such a hemoglobin being present.

The eyes of these 20 patients were examined by the slit lamp; determination of tension and visual fields, and direct and indirect ophthalmoscopy. We found that 15 patients with hemoglobin S-A and 1 with hemoglobin S-S had normal eyes. The remaining four patients had vitreous or retinal abnormalities which could conceivably be the result of their sickle-cell disease. The pertinent facts in each of these cases are documented below.

Report of Cases

CASE 1.—A 33-year-old Negro man first experienced sudden painless diminution of vision in the right eye in 1944. Since that time, he has had numerous recurrences, usually yearly, of this symptom in the right eye, and occasionally in the left eye. The vision would return to normal in two or three weeks. In April, 1956, the patient again had sudden diminution of vision in the right eye. Since then, vision has been light perception with poor projection. A massive vitreous hemorrhage is present and has persisted. A secondary iritis was noted for the first time. The tension dropped to 9 mm. Hg (Schiøtz), where it has remained.

In the left eye, the vision was 20/20 −1, and J_1 type was read at 18 in. without correction. Tension in this eye remained at 19 mm. Hg (Schiøtz).

Upon examination with the slit lamp, the left eye had a normal anterior segment. The right eye had a questionable aqueous ray. Fine keratic precipitates were observed on the corneal endothelium. The lens was normal.

Upon ophthalmoscopic examination with the pupil dilated, the right eye had a black reflex because of the vitreous hemorrhage. The left eye (Fig. 2) had a normal disc and macula. The arterial tree appeared normal. The veins were dilated and tortuous throughout the entire retina. Between 3 and 5 o'clock in the far temporal periphery a large area of chorioretinal atrophy was seen. Similar areas were also noted at 12:30, 1:30, 9:30, and 10 o'clock in the far periphery, but they were much smaller than the one between 3 and 5 o'clock. Hemorrhages, exudates, periphlebitis, or sheathing of the arteries or veins were not found. The atrophic areas at 12:30 and 1:30 had some glial tissue extending into the vitreous from them.

This patient's past medical history revealed that he had had catarrhal jaundice in 1937. On general physical examination his liver and spleen were felt to be enlarged. Teeth, ears, nose and throat, and genitourinary tract were normal.

Electrophoresis demonstrated that he had hemoglobins C and S. The roentgenograms of the chest, tibia, and fibula were normal. Roentgenograms of the skull showed generalized mottling which was felt to be compatible with sickle-cell disease. Skin tests for brucellosis, lymphopathia venereum, and histoplasmosis were negative. A positive skin test to O. T., 1:10,000 strength, was found. The serologic test for syphilis was negative. Cephalin flocculation was 1+; thymol

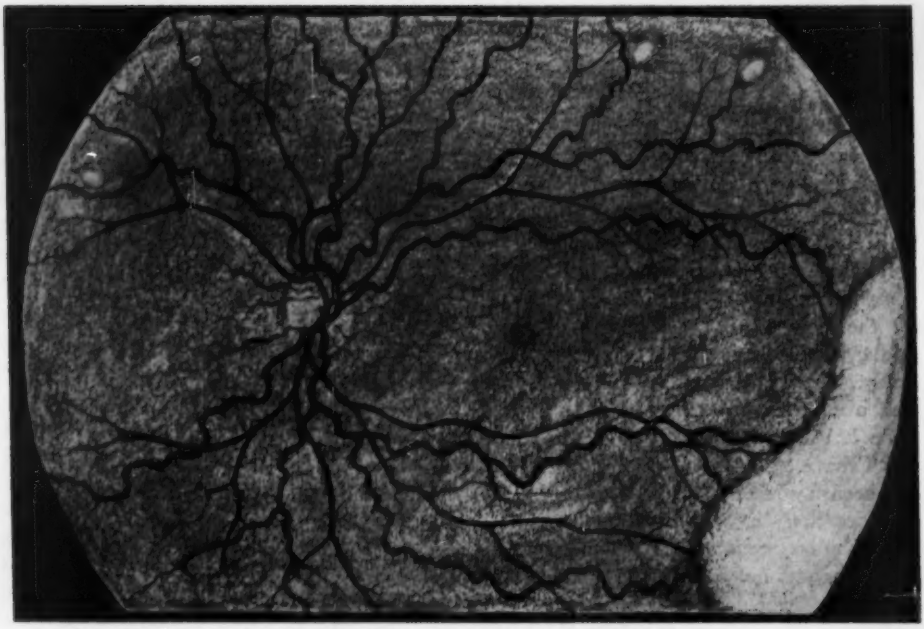

Fig. 2 (Case 1).—Fundus of the left eye, illustrating dilated and tortuous veins, normal arterioles, and areas of chorioretinal atrophy, some of the latter having glial proliferation.

turbidity, 7.5 units, and prothrombin time, 14.3 seconds, with a control of 12.5 seconds. Cutler sedimentation rate was 0 mm. per hour (corrected).

Case 2.—A 28-year-old Negro man had a sudden diminution of vision, pain, and photophobia in the right eye in 1952. During the following six months his vision gradually improved until it became as good as that in the left eye. In 1954 vision again diminished without pain. At that time a diagnosis of vitreous hemorrhage was made. The vision gradually returned to its previous state. There are no eye complaints at the present time. Presently vision in the right eye is 20/25 −1, and J_1 type was read at 18 in., and in the left eye vision was 20/20 −1, and J_1 type was read at 18 in. A complete eye examination was normal except for ophthalmoscopic examination of the right eye. The retina, 1 D. D. above and temporal to the disc, contained a healed area of chorioretinitis which was 2 D. D. in size. Vessels, disc, and macula were normal. A scotoma was plotted on the tangent screen which was obviously the result of this healed area of chorioretinitis.

Electrophoresis revealed that this patient had hemoglobins S and A. No other abnormality was found on general physical examination. No foci of infection could be found. The serologic test for syphilis was negative. He had a positive skin test to O. T. at 1:1000 dilution. Chest roentgenogram was normal. No other significant laboratory test demonstrated an abnormality.

Case 3.—A 34-year-old man of Greek origin had never had any ocular symptoms. Eyes were normal except for the left fundus in the far periphery at 12:30 and 5:30. These two areas, about ½ D. D. in size, were hyperpigmented and had glial tissue in them. The remainder of the fundus was entirely normal.

Electrophoresis revealed the hemoglobin to be S-S. No other symptom, physical finding, or laboratory test was found to

have an etiological relationship to the retinal findings.

CASE 4.—A 37-year-old Negro woman was a sibling of Case 1. She never had had any ocular difficulties. Eye examination revealed completely normal eyes except for the right fundus. On ophthalmoscopic examination one noted that all vessels coming off the disc were markedly tortuous for a short distance. They then became normal.

Electrophoresis revealed hemoglobins S and A. No other facts in the patient's history, no physical finding, nor any laboratory test was found which could account for the abnormal vessels in the right retina.

Comment

On analyzing a very comprehensive report on recurrent intraocular hemorrhage due to tuberculosis in 31 young adults, by Elliot,[22] we could find no patient with lesions similar to those of our Case 1, the case with sickle-cell hemoglobin C disease. Ten of Elliot's patients had tortuous veins, but only in the periphery. Sixteen of his cases had dilated veins, but they were dilated only in the mid- or far periphery. Thirteen of his cases had perivascular exudates. Our Case 1 had dilated and tortuous veins in the retina from the disc out to the far periphery. The dilation and tortuosity were most marked. Our Case 1 had no perivascular exudates, and, lastly, the areas of chorioretinal atrophy were not like those one sees resulting from chorioretinitis but such as one would expect if the entire blood supply were completely blocked. They were clean white areas, with little if any pigment. Although this patient had a positive skin test to O. T., we do not feel that tuberculous infection or sensitivity were etiologic factors in these eye lesions.

We do not feel that Cases 2, 3, and 4 have retinal findings which are with any certainty due to sickle-cell disease. One could postulate that in Case 2 a local chorioretinis is merely present, perhaps the result of the tuberculin sensitivity. In Case 3 the focal changes were so small that it is questionable that they were the result of a generalized disease. In Case 4 a developmental variation of the retinal vessels in one eye may be present.

Venous occlusion can cause varices and aneurysms, and these are frequently followed by hemorrhage into the vitreous.[22] Focal necrosis may occur in scattered areas, causing chorioretinal atrophy. This most certainly occurred in Case 1. Infarction of the choroid as well as of the retina was present. The ocular changes described in Cases 2, 3, and 4 may be the result of sickle-cell disease, although we feel that they are not, for reasons already given.

Conclusion

Of 20 patients with sickle-cell disease for whom electrophoresis of the hemoglobin was performed, 4 had intraocular abnormalities. Three of these four, one with S-S hemoglobin and the other two with S-A hemoglobin, had intraocular lesions which may or may not have been the result of their abnormal hemoglobin. The remaining patient, who had S-C hemoglobin, exhibited characteristics of Eales' disease, as had one of the two previously mentioned cases of S-A hemoglobin. This patient with S-C hemoglobin had such a unique picture in his visible fundus that we feel it was the result of his abnormal hemoglobin.

Summary

Recurrent vitreous hemorrhages (Eales' disease) has, in the past, been ascribed to many etiologic factors. Henry and Chapman recently related the entity and other intraocular changes to sickle-cell disease. The abnormalities of stasis, dilatation of the veins, hemorrhages, and infarction are secondary to the relatively inflexible, misshapen, sickled cells. Of the numerous reports pertaining to sickle-cell hemoglobin C disease, only Smith and Conley and Hannon have commented on its probable relationship to vitreous hemorrhages.

In our study of 20 cases of sickle-cell disease diagnosed by electrophoretic and in

vitro sickling methods, 4 demonstrated abnormal intraocular changes.

Case 1 gave an extended history of recurrent vitreous hemorrhages associated with dilated tortuous veins, peripheral chorioretinal atrophy, secondary iritis, and hypotony. Other possible causes were eliminated, and the patient's sickle-cell hemoglobin C disease was designated as the underlying causal agent.

Case 2 undeniably represented an example of Eales' disease, but a healed chorioretinitis seemingly pointed away from his sickle-cell trait (hemoglobins S and A) as the cause of his lesion, although the latter possibility was by no means excluded.

Case 3 demonstrated two small areas of glial tissue with pigmentation in the left fundus, which were possibly related to sickle-cell anemia.

Case 4, a sibling of Case 1 and showing the trait (hemoglobins S and A), merely had tortuosity of the right fundic vessels.

This study, in conjunction with the observations of Smith and Conley and Hannon, suggests that there is a causal relationship between recurrent intraocular hemorrhage and sickle-cell disease, especially of the hemoglobin S-C variety.

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REFERENCES

1. Eales, H.: Cases of Retinal Hæmorrhage, Associated with Epistaxis and Constipation, Birmingham M. Rev. 3:262-273, 1880.

2. Young, C. A.: Recurrent Hemorrhages into Retina and Vitreous: Calcium Deficiency as a Possible Cause, Am. J. Ophth. 13:125-131 (Feb.) 1930.

3. Marchesani, O.: Thrombangiitis obliterans am Auge, Arch. Augenh. 109:124-138, 1935.

4. Duke-Elder, W. S.: Text Book of Ophthalmology, Vol. 3, St. Louis, The C. V. Mosby Company, 1941, p. 2602.

5. Axenfeld, T., and Stock, W.: Über die Bedeutung der Tuberkulose in der Aetiologie der intraokularen Hämorrhagien und der proliferierenden Veränderungen in der Netzhaut, besonders über Periphlebitis retinalis bei Tuberkulösen, Klin. Monatsbl. Augenh. 49:28-34, 1911.

6. Cook, W. C.: A Case of Sickle-Cell Anemia with Associated Subarachnoid Hemorrhage, J. Med. 11:541 (Dec.) 1930.

7. Edington, G. M., and Sarkies, J. W. R.: Two Cases of Sickle-Cell Anemia Associated with Retinal Lesions, Tr. Roy. Soc. Trop. Med. & Hyg. 46:59-62 (Jan.) 1952.

8. Henderson, A. B.: Sickle-Cell Anemia: Clinical Study of 54 Cases, Am. J. Med. 10:757-765 (Dec.) 1950.

9. Harden, A. S.: Sickle-Cell Anemia: Changes in the Vessels and in the Bones, Am. J. Dis. Child. 54:1045-1051 (Nov.) 1937.

10. Henry, M. B., and Chapman, A. Z.: Vitreous Hemorrhage and Retinopathy Associated with Sickle-Cell Disease, Am. J. Ophth. 38:204-209 (Aug.) 1954.

11. Smith, E. W., and Conley, C. L.: Clinical Features of the Genetic Variants of Sickle Cell Disease, Bull. Johns Hopkins Hosp. 94:289-318 (June) 1954.

12. Hannon, J. F.: Personal communication to the authors.

13. Neel, J. V.; Kaplan, E., and Zuelzer, W. W.: Further Studies on Hemoglobin C: I. A Description of 3 Additional Families Segregating for Hemoglobin C and Sickle Cell Hemoglobin, Blood 8:724-734 (Aug.) 1953.

14. Kaplan, E.; Zuelzer, W. W., and Neel, J. V.: Further Studies on Hemoglobin C: II. The Hemotologic Effects of Hemoglobin C Alone and in Combination with Sickle Cell Hemoglobin, Blood 8:735-746 (Aug.) 1953.

15. Smith, E. W., and Conley, C. L.: Filter Paper Electrophoresis of Human Hemoglobins with Special Reference to the Incidence and Clinical Significance of Hemoglobin C, Bull. Johns Hopkins Hosp. 93:94-106 (Aug.) 1953.

16. Hays, E. F., and Engle, R. L., Jr.: Sickle Cell Hemoglobin C Disease, Ann. Int. Med. 43: 412-418 (Aug.) 1955.

17. Murphy, R. C., Jr., and Shapiro, S.: The Pathology of Sickle Cell Disease, Ann. Int. Med. 23:376-397 (Sept.) 1945.

18. Singer, K.: The Pathogenesis of Sickle Cell Anemia: A Review, Am. J. Clin. Path. 21:858-865 (Sept.) 1951.

19. Kimmelstiel, P.: Vascular Occlusions and Ischemic Infarctions in Sickle Cell Disease, Am. J. M. Sc. 216:11-19 (July) 1948.

20. Wintrobe, M. M.: Clinical Hematology, Ed. 3, Philadelphia, Lea & Febiger, 1951, pp. 607-628.

21. Itano, H.; Bergren, W. R., and Sturgeon, P.: Identification of a 4th Abnormal Human Hemoglobin, J. Am. Chem. Soc. 76:2278 (April) 1954.

22. Elliot, A. J.: Recurrent Intraocular Hemorrhage in Young Adults (Eales' Disease), Tr. Am. Ophth. Soc. 52:811-875, 1954.

Evaluation of Histochemical Techniques for Carbonic Anhydrase in Ocular Tissues

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The recent interest in the role of carbonic anhydrase in the formation of the aqueous humor [1-3] stimulated the present attempt to demonstrate the presence and location of this enzyme in ocular tissues by histochemical methods.

Carbonic anhydrase is known to be a zinc-containing enzyme.[4] Wistrand [5] first reported the presence of the enzyme in the anterior uvea of the rabbit. This was confirmed by Green and his co-workers [6] in 1955, by Ballantine and Maren,[7] and by Gloster and Perkins [8] in 1955. These authors employed biochemical techniques in order to demonstrate the presence of carbonic anhydrase.

The demonstration of carbonic anhydrase in histological sections by histochemical methods has been reported by Kurata.[9] The tissues utilized in the original experiments were the parietal cells of the gastric mucosa and the red blood cells of the rat. A positive reaction was indicated by the deposition of a fine brown precipitate of manganous oxide in the areas of carbonic anhydrase activity. In 1954, Goebel and Puchtler [10] described unsatisfactory attempts to demonstrate the localization of the enzyme in paraffin sections of the epithelium of the kidney tubules and the epithelial cells of the gastric mucosa of the rat, according to the method originally outlined by Kurata. These authors modified the Kurata method and by use of frozen sections reported the sucessful demonstration of the enzyme in sections of the kidney and gastric mucosa of the rat. De Berardinis and Gaipa [11] were able to localize carbonic anhydrase in sections of the iris and ciliary body of the rabbit eye by the Kurata technique, noting especially that the reaction appeared to be inhibited by the intravenous administration of acetazolamide prior to killing of the animal and prior to the histological preparation of the tissues. In none of the above instances were any enzyme control studies reported. The purpose of the present study was to evaluate the results of histochemical methods for zinc localization and to determine the extent to which the Kurata method and its modifications might be used to demonstrate carbonic anhydrase in histological sections of the iris and ciliary body of the rabbit eye.

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Materials and Methods

In evaluation of the zinc methods, gastric mucosa, iris, and ciliary body tissue were employed. The two histochemical methods for zinc localization which were utilized were were those of Mendel and Bradley [12] and Okamoto.[13]

The uveal tissues studied were obtained from the eyes of albino rabbits weighing 4 to 6 lb. The animals were killed by air injection and placed in an upright position so that most of the blood drained from the head. The aqueous was removed from the anterior chamber and replaced with air to insure removal of most of the residual blood. After enucleation, the iris and ciliary body were removed in toto, with use of the posterior approach described by Green et al.[2] All tissues were fixed in acetone for one hour prior to embedding in paraffin.

Fig. 1.—Normal tissue section from iris and ciliary processes of albino rabbit eye treated with cobalt chloride-ammonium sulfide variation of Kurata technique. Paraffin section. Cross section cut at 20μ.

One hundred fifty cross sections of iris and ciliary body cut at 20μ and 25μ were used for the original Kurata method and the cobalt chloride-ammonium sulfide modification of this technique. One hundred fifty frozen preparations of flat sections of iris and ciliary body were cut at 20μ for the Goebel-Puchtler modification.

Controls were prepared according to the methods suggested by Gomori.[14] Sections untreated by any reagents and sections treated by omission of one or more reagents were the primary control. Acetazolamide (Diamox),* a carbonic anhydrase inhibitor, was injected intravenously into the rabbit (20 mg. per kilogram body weight) 30 minutes prior to killing the animal.[6] Iris and ciliary body were also incubated at 37 C in a solution of acetazolamide (50 mg. per cubic centimeter) for 15, 30, and 45 minutes and at room temperature for 60 minutes. Other methods to inhibit enzyme activity included the treatment of tissue with oxidizing agents (3% hydrogen peroxide for 5 to 10 minutes; 0.1% potassium permanganate for 14 hours), reducing agents (5% sodium sulfate for 14 hours), and copper sulfate (14 hours) prior to sectioning and staining. Ninety-five per cent alcohol for 1 hour, boiling water for 5 to 10 minutes, or 2 N hydrochloric acid for 10 to 15 minutes were also employed in an attempt to destroy the enzyme.

* Supplied by Dr. James F. Gallagher, Lederle Laboratories, Pearl River, N. Y.

Results

The Mendel and Bradley and Okamoto methods for the localization of zinc in the gastric mucosa and the iris and ciliary body of the rabbit yielded negative results in all tissues. One hundred fifty tissues were prepared for each method. Kurata's technique, as originally proposed, yielded negative results in every tissue studied. The cobalt chloride-ammonium sulfide variation of the Kurata method gave the appearance of a positive reaction in normal tissue (Fig. 1). Scattered clumps of pigment were localized in the ciliary processes and in

Fig. 2.—Tissue section from iris and ciliary processes of albino rabbit eye from animal given intravenous injection of acetazolamide (30 mg. per kilogram body weight). Tissue treated with cobalt chloride-ammonium sulfide variation of Kurata technique. Paraffin section. Cross section cut at 20μ.

some regions of the ciliary body and were sparsely scattered over the anterior surface of the iris. Tissues from rabbits given acetazolamide intravenously (30 mg. per kilogram body weight) failed to show any significant difference in the amount and deposition of precipitate compared with normal sections (Fig. 2). Tissues treated with 2 N hydrochloric acid for 10 to 15 minutes, until they became transparent, yielded a reaction similar to the complete reaction produced on normal tissues. Sections from tissues treated with boiling water, 5 to 10 minutes and tissues treated with 0.1% potassium permanganate or 0.2% copper sulfate for approximately 14 hours yielded negative reactions.

The Goebel and Puchtler modification, involving fresh frozen sections and utilizing cobalt chloride and ammonium sulfide as the principal reagents, yielded a positive reaction when applied to normal tissues. The complete reaction performed on normal tissues showed the presence of clumping of dark masses of black granules which had a tendency to localize on surfaces of the rugose folds of the iris and the crypts between the folds. Black pigment clumps were also located peripherally in the areas of the ciliary processes and around the pupillary border of the iris. The reaction was not constant nor was it characteristic, and it appeared to be entirely superficial.

In every case where the complete reaction was employed, the control sections showed positive results similar to the reaction in normal tissues. Sections taken from iris and ciliary body removed 40 minutes after the intravenous injection of acetazolamide yielded positive reactions, although the precipitate was much more diffuse and the clumps of material were much smaller. Control tissues treated with one of the following: hydrogen peroxide, sodium bisulfite, sodium sulfite, 95% alcohol, or boiling water, or those incubated with acetazolamide in an effort to destroy carbonic anhydrase, gave positive results that were in no way different from those obtained using the complete process on normal tissue. Control tests on normal tissues involving the use of cobalt chloride and the bicarbonate buffer alone showed no reaction. Tests utilizing ammonium sulfide alone showed no reaction. Control tests on normal tissues which were treated with all the agents except sodium bicarbonate gave a positive reaction similar to that obtained when the complete process was employed on normal tissue.

Paraffin sections of rabbit kidney and gastric mucosa were submitted to the above histochemical techniques. Similar equivocal patterns resulted in control sections and in normally treated sections. It is interesting to note that normal tissue sections which were cut at 20μ, deparaffinized with xylene, and mounted showed the presence of intracellular granules similar to those described as constituting a positive reaction. These granules were not removed from any sections passed through xylene or xylene and 100% alcohol or from deparaffinized sections placed in acetone and cleared with xylene. The granules disappeared, however, as soon as the sections were immersed in hydrated alcohol solutions. Although the particles resembled melanin or lipofucsin granules, histochemical tests indicated that they were neither. The tests employed for the detection of lipofucsin pigments consisted of Sudan black reaction, the periodic acid-Schiff reaction, the alkaline silver reaction for melanin, and Schmorl's reaction for lipofucsin.[15]

Comment and Summary

Histochemical methods for demonstration of zinc in the iris and ciliary body of the rabbit yielded negative results. This is consistent with the results of Pearse.[16] It may be concluded either that the sensitivity of the technique used was not great enough or that the metal was not free to react in either case. Attempts to localize carbonic anhydrase in the iris and ciliary body of the albino rabbits using Kurata's original method were unsuccessful. The tissues were

entirely devoid of a precipitate, either extracellular or intracellular. This confirms preliminary findings of Wachstein on kidney tissues.[17] Results obtained with the Gomori modification of the Kurata method were inconsistent. Most of the control sections yielded positive results. The validity of the stain is therefore open to question. The same statements hold true for the Goebel-Puchtler modification of the original method.

It may be helpful to define the chemistry involved in the reactions outlined above. It is postulated that the metallic ion becomes attached to the enzyme site in the form of the bicarbonate. Carbonic anhydrase supposedly acts upon the bicarbonate to precipitate an insoluble metallic carbonate on the tissue at the site of the enzyme, which is not washed away by subsequent treatment. With the use of an oxidizing agent (KIO_4) in the original Kurata method, the attached Mn^{++} ions are oxidized to the brown MnO_2 deposits, which might be identified at the cellular level. In the case of the cobalt modification, the precipitate would be black cobalt sulfide, which could readily be identified in tissue section. All of these presumed reactions depend upon the premise that the metal bicarbonate is bound to the enzyme site and is a substrate for the enzyme action.

That these reactions take place is open to serious question. There is no reason to believe that carbonic anhydrase has any effect on a metallic bicarbonate. Indeed, the literature [18,19] suggests that carbonic acid or carbon dioxide is the immediate substrate of carbonic anhydrase action according to the following equation: $CO_2+H_2O \rightarrow H_2CO_3$. Furthermore, in view of the negative results with control studies, it would seem that the precipitate MnO_2 or CoS is not firmly bound to the tissue but is readily washed away.

A more reasonable assumption of the reactions which occur is as follows:

(1) $MnCl_2+2NaHCO_3 \rightarrow Mn(HCO_3)_2+2NaCl$

(2) $Mn(HCO_3)_2 \leftrightarrows$ (dissociated) $Mn^{++}+2HCO_3-HOH$ (hydrolysis)

(3) $Mn^{++}+2OH^-+H_2CO_3$

(4) $Mn^{++}+2OH^-+KIO_4 \rightarrow MnO_2+KIO_3+H_2O$

(5) H_2CO_3 + carbonic anhydrase $\rightarrow H_2O+CO_2$

In the original Kurata technique the precipitate of manganous oxide is probably washed out of solution during preparation. The soluble $Mn(HCO_3)_2$ probably is present predominantly in the form of Mn^{++} and HCO_3^-. Hydrolysis of such a salt of a weak acid (H_2CO_3) in a relatively weak base [$Mn(OH)_2$] leads to the formation, in small amounts, of $Mn(OH)_2$ and H_2CO_3. Reaction with KIO_4 at this point merely results in the oxidation of the $Mn(OH)_2$ or Mn^{++} to MnO_2, which deposits as a brownish precipitate. There is no reason to believe that the Mn^{++} or $Mn(OH)_2$ are specifically localized at the enzyme site, but it is more likely that they are uniformly distributed throughout the medium. Hence, the brown MnO_2 should also be more or less uniformly dispersed in the medium and rather easily washed out. The H_2CO_3, on the other hand, in the presence of the enzyme is converted into H_2O and CO_2. Similarly with the $CoCl_2$-$(NH_4)_2S$ system, CoS is deposited instead of MnO_2. It is, therefore, clear that if these reactions are correct as formulated then the experimental conditions are incompatible with the histochemical detection of carbonic anhydrase. The above reactions also may explain the reason why acetazolamide is ineffective in inhibiting the reactions. Carbonic anhydrase is not essential in locating the metallic precipitate at the enzyme site.

The nature of the granules present in normal sections cut at 25μ, although tested by several histochemical methods, remains obscure. Hydration of these granules caused them to disappear. This suggests the possibility that the alcohol used in the paraffin process causes certain protein components of the cellular cytoplasm to become denatured. These granules could be mistaken for the precipitates described in the original Kurata procedure.

Conclusions

Techniques for the histochemical demonstration of carbonic anhydrase were applied to the iris, ciliary body, kidney, and gastric mucosa of the rabbit. None of these techniques produced constant results in the tissues tested, and the results were not different from those obtained after the destruction of the enzymes by standard methods. None of the techniques showed definite inhibition of the enzyme by acetazolamide either intravenously administered or when the tissues were incubated with the inhibitor. A discussion of the chemical reactions probably involved is presented.

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REFERENCES

1. Becker, B.: Decrease in Intraocular Pressure in Man by a Carbonic Anhydrase Inhibitor, Diamox, Am. J. Ophth. 37:13-15, 1954.

2. Green, H.; Capper, S. A.; Bocher, C. A., and Leopold, I. H.: Effect of Acetazoleamide (Diamox) on Carbonic Anhydrase Activity of Anterior Uvea of the Rabbit Eye, A. M. A. Arch. Ophth. 52:758-762, 1954.

3. Breinin, G. M., and Görtz, H.: Carbonic Anhydrase Inhibitor Acetazoleamide (Diamox): A New Approach to the Therapy of Glaucoma, A. M. A. Arch. Ophth. 52:333-348, 1954.

4. Clark, A. M., and Roughton, F. J. W., in Sumner, J. B., and Myrbach, K.: The Enzymes, New York, Academic Press, Inc., 1951, Vol. 1, Pt. 2, Ch. 43, p. 1250.

5. Wistrand, P. J.: Carbonic Anhydrase in the Anterior Uvea of the Rabbit, Acta physiol. scandinav. 24:144-148, 1951.

6. Green, H.; Bocher, C. A.; Calnan, A. F., and Leopold, I. H.: Carbonic Anhydrase and the Maintenance of Intraocular Tension, A. M. A. Arch. Ophth. 53:463-473, 1955.

7. Ballantine, E. J., and Maren, T. H.: Carbonic Anhydrase Activity and the Distribution of Diamox in the Rabbit Eye, Am. J. Ophth. 40:148-155 (Nov., Pt. 2) 1955.

8. Gloster, J., and Perkins, E. S.: Carbonic Anhydrase in the Lens and in the Ciliary Body and Iris of Albino Rabbits, J. Physiol. 130:665-673, 1955.

9. Kurata, Y.: Histochemical Demonstration of Carbonic Anhydrase Activity, Stain Technol. 28: 231-233, 1953.

10. Goebel, A., and Puchtler, H.: Zur Darstellung der Carboanhydrase im histologischen Schnitt, Naturwissenschaften 41:531-532, 1954.

11. de Berardinis, E., and Gaipa, M.: Influenza dell'acetazoleamide sull'anidrasi carbonica del corpo ciliare e sul meccanismo di formazione dell'umor acqueo, Boll. Soc. ital. biol. sper. 30:1314-1316, 1954.

12. Mendel, L. B., and Bradley, H. C.: Experimental Studies on the Physiology of the Molluscs, Am. J. Physiol. 14:313, 1905.

13. Okamoto, K.: Biologische Untersuchungen der Metalle: VI. Histochemischer Nachweiss einiger Metalle in den Geweben, besonders in den Nieren und deren Veränderungen, Tr. Soc. Path. Japan 32:99-105, 1942.

14. Gomori, G.: Microscopic Histochemistry, Chicago, The University of Chicago Press, 1952.

15. Pearse, A. G. E.: Histochemistry Theoretical and Applied, Boston, Little, Brown & Company, 1953, Ch. 15.

16. Pearse, A. G. E.: Histochemistry Theoretical and Applied, Boston, Little, Brown & Company, 1953, Ch. 16., p. 376.

17. Wachstein, M.: Histochemical Staining Reactions of the Normally Functioning and Abnormal Kidney, J. Histochem. 3:246-270, 1955.

18. Roughton, F. J. W.: Recent Work on Carbon Dioxide Transport by Blood, Physiol. Rev. 152:41-196, 1935.

19. Pitts, R. F.: Mechanism for Stabilizing the Alkaline Reserves of the Body, Harvey Lect. 48: 172-209, 1953.

Comparative Electroretinographic Studies in Congenital Night Blindness and Total Color Blindness

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In the analysis of the human electroretinogram, the study of subjects with congenital night blindness and total color blindness is of great value. The absence of specific electroretinographic components in these anomalies simplifies the complex pattern of response, allows a more detailed investigation of the remaining components, and aids in the analysis of the photopic-scotopic nature of the different waves. However, the few investigations which deal with the electroretinogram in congenital night blindness and total color blindness have studied each condition separately; therefore, no direct comparison has been made between their electroretinographic responses.

The purpose of this study is to investigate quantitatively the influence of dark-adaptation and stimulus intensity on the electroretinogram of normal, congenitally night-blind, and totally color-blind subjects,* examined under identical experimental conditions.

Subjects

The night-blind subject is a 28-year-old married white woman. She has been aware of poor night vision in both eyes since childhood, nonprogressive in nature. A sister is similarly affected. There is no other family history of night-blindness. The parents were first cousins. The patient also notes that her left eye has always been "crossed."

Visual acuity in the right eye was 20/25 with a −2.0 D. sph⊂−1.75 D. cyl, ax 105 correction. Visual acuity in the left eye was 20/60 with −3.50 spheres, and an intermittent exotropia was present. Biomicroscopy was negative, except for the presence of a small anterior polar opacity in the left lens. Fundus examination of both eyes disclosed a fine pigment dispersion in an area one disk diameter in width adjacent to the temporal border of each disk. The optic disks, retinal vessels, maculae, and fundus periphery were normal. No abnormalities were found on visual field examinations with a 3 mm. white target at 330 mm. under standard illumination. (The right eye was used for the electroretinographic studies.)

The totally color-blind subject is a 38-year-old married white woman. Color blindness, photophobia, and defective vision have been present as far back as the subject can remember. Nystagmus was marked during childhood but has gradually disappeared, with a concomitant improvement in visual acuity. The mother is reported to have had normal color vision. No information is available regarding the father's color vision. The patient was recently operated on to correct a deviation of the left eye.

The corrected visual acuity in both eyes was 20/200 with −3.00 spheres. A left exotropia was present. Internal examination of both eyes, including fundus study, was essentially negative. (The right eye was used for the electroretinographic studies.)

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*The two subjects with congenital retinal anomalies were made available by Dr. Louise Sloan of the Wilmer Ophthalmological Institute (The Johns Hopkins Hospital).

Three normal subjects (Subjects 1, 2, and 3), with no ocular complaints or evidence of ocular pathology, were also studied.

The results of psychophysical testing in these subjects were as follows:

A. H-R-R Pseudoisochromatic Plates.—The normal and night-blind subjects identified all plates correctly. The color-blind subject identified only Plate 20 correctly, on the basis of a brightness difference between number and background.

B. Flicker Fusion Frequency (FFF).—This was determined with a stimulus patch of 1 degree, and a luminance of about 100 millilamberts, in the light-adapted state. Testing was performed with the patch fixated centrally and at 15 and 30 degrees in the nasal field. Under these conditions, the FFF of normal subjects was found to be 40 per second and above. The FFF of the night-blind subject was 40 per second, but the color-blind subject did not exceed an FFF of 20 per second. This is in accord with findings in a previously reported case of total color blindness.[1]

C. Purkinje Shift.—This test was performed with blue and red paper on a black background. In bright light, the normal subjects saw the red patch brighter than the blue. Under poor illumination, after a period of dark adaptation, the normal subjects saw the blue patch brighter than the red. This shift in sensitivity from red to blue light (Purkinje shift) is due to the change from photopic activity, with its greater sensitivity for the longer wavelengths, to scotopic activity, with its greater sensitivity for the shorter wavelengths.

The Purkinje shift was absent in the color-blind subject; the blue patch was reported as the brightest regardless of adaptation state and illumination. In the night-blind subject the Purkinje shift was also absent, and the red light was brightest under all conditions.

D. Dark Adaptation.—This test was performed with the Goldmann adaptometer, after a 10-minute preadaptation to a 420 millilambert light source in the integrating sphere. The test patch was 11 degrees in diameter, with its center about 11 degrees from fixation.

The dark-adaptation curves of the congenital night-blind, total color-blind, and a normal subject (Subject 1) are demonstrated in Figure 1. The adaptation curve in the normal subject revealed two branches, separated by a "break" at about eight minutes. The first portion of the curve is identified with photopic function, and the second portion, with scotopic function.[2]

The color-blind subject showed a normal threshold after 40 minutes of dark adaptation. During the first few minutes, however, the rate of adaptation appeared to be more rapid than that of the normal subject. This may be attributed to the decreased effectiveness of the preliminary light adaptation in this subject, due to the blinking and upward rolling of the eyes attendant upon intense photophobia.

The night-blind subject reached a final threshold after 40 minutes of dark adaptation which was about 3 log units above the normal scotopic threshold. There was no evidence of a "break" in the curve during the critical time of 6 to 10 minutes. A slightly elevated cone threshold was found by threshold determinations with red light

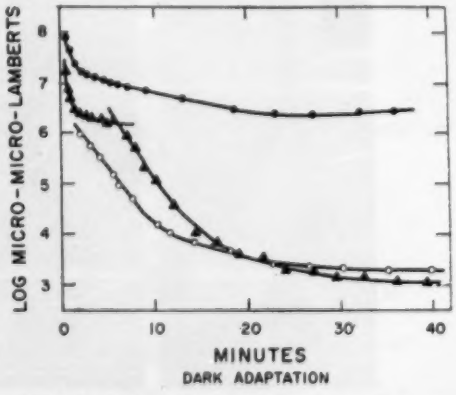


Fig. 1.—Dark-adaptation curves in normal subject 1 (triangle), a congenitally night-blind subject (black circle), and a totally color-blind subject (white circle).

centrally fixated and with the nyctometer test (Comberg), as performed with the Goldmann adaptometer.

Apparatus

Since a detailed description of the apparatus has been included in a previous paper,[3] only the main points will be reviewed here. The electroretinographic potentials were picked up from the cornea by means of a contact lens electrode and led to a capacity-coupled preamplifier which was connected with one of the direct-coupled main amplifiers in a double-beam cathode-ray oscilloscope. The over-all time constant was sufficiently high to avoid measurement errors due to the frequency response of the amplifier system. (The lower limit of frequency range was less than one per second.) The light stimuli produced by an electronic light stimulator were flashes of about 10 microseconds duration. Peak luminance was about 6×10^7 millilamberts and is referred to as intensity 100 (arbitrary units). The stimulus patch had a diameter of 19 degrees and was equipped with a small central red fixation light. Red light stimuli were produced by means of standard Wratten filter No. 29. Neutral filters were used to vary intensity. The light stimulus was simultaneously recorded by a photo-cell and the second channel of the cathode-ray oscilloscope.

Experimental Procedure

All electroretinographic records were obtained in complete darkness from the right eye of the subject, after maximal dilation with cyclopentolate (Cyclogyl) hydrochloride 1% and phenylephrine (Neo-Syneph-

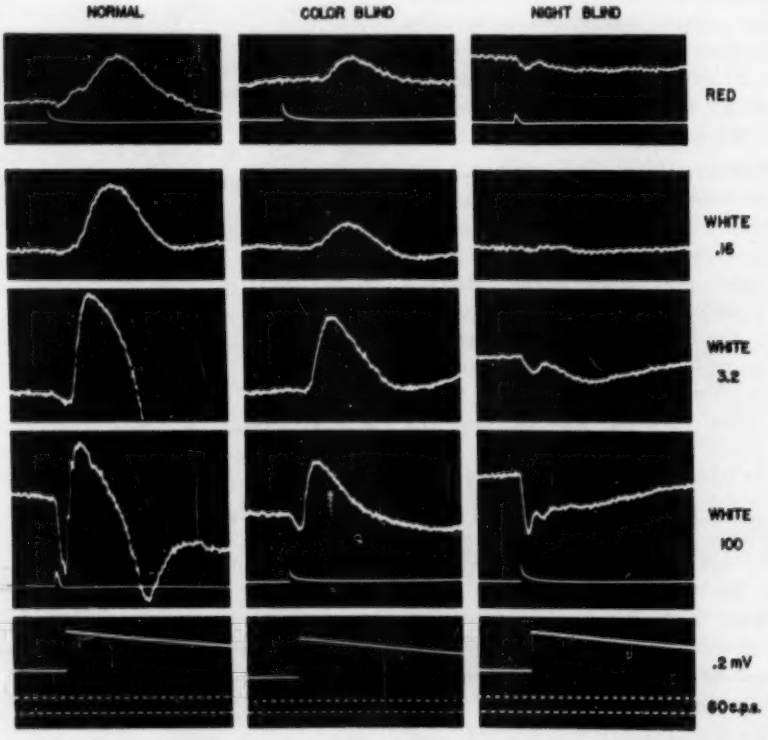


Fig. 2.—The electroretinogram in normal (Subject 2), totally color-blind, and congenitally night-blind subjects, in response to white light stimuli of different intensity and to a red light stimulus, under conditions of dark adaptation. The color-blind subject lacks the photopic x-wave, while the night-blind subject lacks the scotopic b-wave.

rine) hydrochloride 10%. In studying the influence of stimulus intensity on the electroretinogram, the recordings were begun after 30 minutes of dark adaptation following a previous exposure to the average room illumination of 8 ft-c. For every given intensity several responses were obtained and the mean value was calculated. The effect of dark adaptation was studied by recording the electroretinogram at different times after a period of 10 minutes of light adaptation. (The adapting field was 90 degrees in diameter, with a uniform luminance of about 1000 millilamberts.)

The evaluated material of this study includes 545 records.

Results

The photopic and scotopic components of the human electroretinogram can be separated most clearly with red light stimuli. As shown in Figure 2, the electroretinogram elicited by red light stimuli normally consists of an initial negative response (a-wave) followed by two positive responses: a more rapid wave (photopic x-wave) and a comparatively slow wave (scotopic b-wave). The color-blind subject lacks the x-wave, whereas the night-blind subject lacks the b-wave. Therefore, each anomaly in this study is characterized by a single different positive wave.

In contrast to the response to red stimuli, the electroretinographic response to white light flashes shows less temporal separation between the two positive components: The b-wave occurs during the x-wave. However, a clear differentiation between x-wave and b-wave in response to white light may be seen in normal subjects during the early period of dark adaptation (Fig. 3). The low magnitude of the b-wave under these

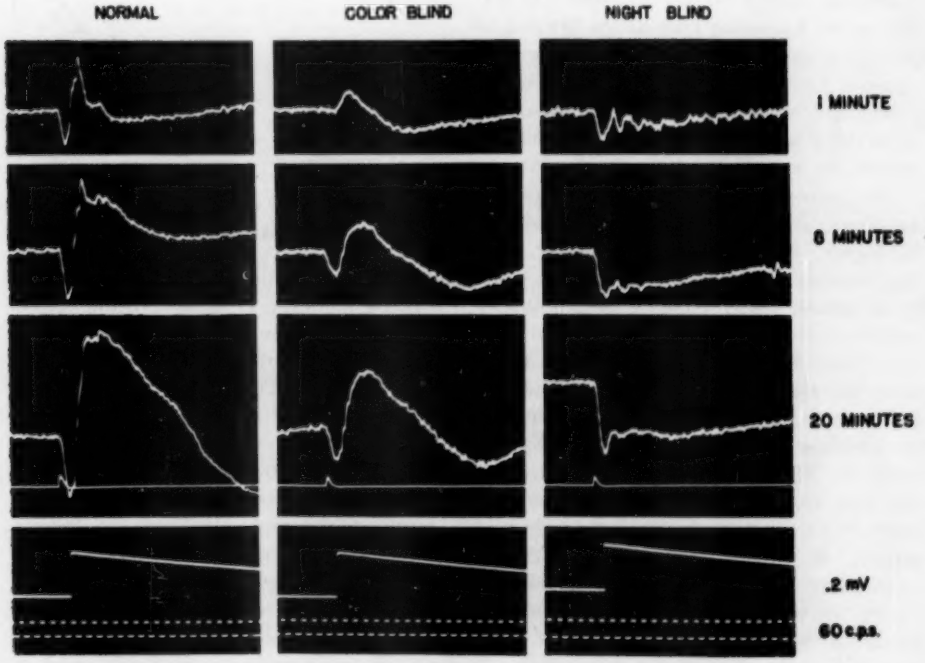


Fig. 3.—The electroretinogram in normal (Subject 1), totally color-blind, and congenitally night-blind subjects, in response to a standard white light stimulus (intensity 100), after 1, 8, and 20 minutes of dark adaptation, following a preliminary light adaptation. The color-blind subject lacks the photopic x-wave, while the night-blind subject lacks the scotopic b-wave.

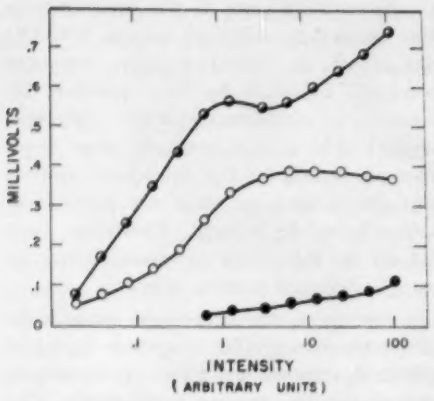


Fig. 4.—The influence of stimulus intensity on the amplitude of the positive electroretinographic response in normal Subject 2 (black-and-white circle), a totally color-blind subject (white circle), and a congenitally night-blind subject (black circle). Each point is the mean value of three to nine responses. The second rise in the curve of the normal subject, which is a function of the x-wave, is absent in the curve of the color-blind subject.

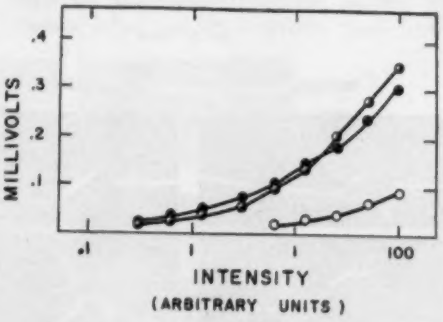
conditions allows the x-wave, which is riding on the ascending limb of the b-wave, to project above it. In keeping with the responses noted with red light stimuli, the color-blind subject retains the b-wave but lacks the x-wave and the night-blind subject retains the x-wave but lacks the b-wave.

The influence of stimulus intensity on the amplitude of the positive responses* is shown in Figure 4. In the normal subject with logarithmically increasing intensities there is an almost linear increase of amplitude, which arrives at a first maximum with rather high intensities. When higher intensities are used, a second increase of amplitude occurs, which is presumably due to the addition of the x-wave to the positive response. This assumption is supported by the fact that in the color-blind subject, where the x-wave is absent in the response pattern, the second increase in amplitude is similarly lacking. Furthermore, the intensity curve of the night-blind subject reveals an increase in amplitude of its positive component (the isolated x-wave) in the same range of high intensities that elicits the second rise in amplitude in the normal subject.

The intensity function of the a-wave, demonstrated in Figure 5, is identical in the normal and night-blind subjects. The a-wave of the color-blind subject shows a similar function, but its amplitude is well below that of the normal and night-blind subjects. The reduction in amplitude is equivalent to a shift of 1 log unit toward the higher intensity stimuli.

The changes in the electroretinogram during dark adaptation in response to a strong standard light stimulus are shown

Fig. 5.—The influence of stimulus intensity on the amplitude of the negative electroretinographic response (a-wave) in normal Subject 2 (black-and-white circle), a totally color-blind subject (white circle), and a congenitally night-blind subject (black circle). Each point is the mean value of three to nine responses.



by original records (Fig. 3) and demonstrated graphically (Fig. 6). In the normal subject the amplitude of the a-wave increases during dark adaptation in a characteristic manner. There is an initial increase during the first 2 minutes which reaches a plateau, followed by a second increase beginning at about 6 minutes and leveling off at about 20 minutes. Surprisingly, the a-wave of the night-blind subject follows this normal pattern. The a-wave of the color-blind subject, however, begins with a very low amplitude, which then increases steadily during the course of dark adaptation. There is no evidence of a "break" in the curve during the first 10 minutes, which is manifest in both normal and night-blind subjects.

* The amplitude of the positive response was measured from the bottom of the a-wave.

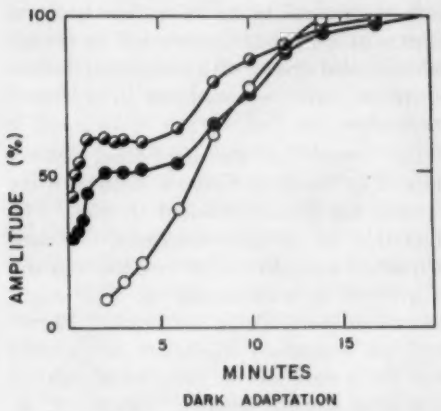


Fig. 6.—The influence of dark adaptation on the negative electroretinographic response (a-wave) of normal Subject 1 (black-and-white circle), a totally color-blind subject (white circle), and a congenitally night-blind subject (black circle). Standard white light stimulus (intensity 100). A "break" is present in the curve of the normal and night-blind subjects at about six minutes which is absent in the color-blind subject.

The increase in amplitude of the positive waves of the normal and color-blind subjects during dark adaptation parallels the behavior of their respective a-waves. There is a steady increase during the first 20 minutes of dark adaptation in both subjects, but a definite "break" is present in the normal subject at about 6 minutes which is absent in the color-blind subject. The positive wave of the night-blind subject shows a paradoxical decrease in amplitude from 45 seconds to 6 minutes of dark adaptation, followed by a plateau (Fig. 7). This is in contrast to the increase in amplitude noted in the a-wave under the same conditions.

Comment

There are two positive potentials in the human electroretinogram: x-wave and b-wave. The functional interpretation of these waves as photopic and scotopic responses, respectively, is based upon their spectral sensitivities,[4-7] their flicker fusion frequencies,[8-11] and their different behavior during dark adaptation.[12-14] The study of the retinal anomalies of congenital night blindness and total color blindness has been particularly valuable in demonstrating this differentiation.

In three cases of congenital night blindness (Schubert and Bornschein,[15] Armington and Schwab [16]), and in the present case, the positive wave in the response demonstrated the characteristics of the x-wave. The intensity curve of the positive wave in the present study showed a gradual slope similar to the x-wave of normal subjects isolated with red light stimuli (Armington and Thiede [17]). The decrease in amplitude of this positive wave during the first few minutes of dark adaptation was also in keeping with the normal behavior of the x-wave (Armington [18]). Furthermore, a separate study of the electroretinographic response of this night-blind subject to flickering stimuli (Goodman and Iser [11]) afforded additional proof of the identity of

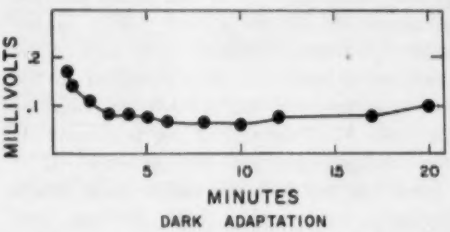


Fig. 7.—The influence of dark adaptation on the positive electroretinographic response (x-wave) of the congenitally night-blind subject. Standard white light stimulus (intensity 100).

the positive wave with the x-wave and confirmed the findings first reported by Bornschein and Schubert [9] in their flicker-electroretinogram studies of another congenitally night-blind subject.

The temporal course of the positive wave in the congenitally night-blind subject was also characteristic of the x-wave, since the implicit time was consistently about 50 msec. for a wide range of low- and moderate-intensity stimuli.[15-18] However, with the highest intensity stimuli there was an abrupt change to an implicit time of 32-36 msec. This same implicit time was characteristic of a hump, noted with moderate intensities, which apparently determined the peak of the response with the highest intensities.

(The complex appearance of the x-wave was manifest during the early minutes of dark adaptation by the appearance of multiple humps.)

Total color blindness has been studied electroretinographically in two subjects. Dodt and Wadensten [19] have reported one subject in whom the response to flickering stimuli consisted only of a scotopic component, and this has been confirmed in the present subject (Goodman and Iser [11]). A detailed study of the response to individual light stimuli in another totally color-blind person was made by Vukovich.[20] Examination disclosed a scotopic b-wave, with complete absence of the photopic x-wave, and these findings have been repeated here. Consequently, the intensity function of the positive wave in the present case failed to show the second rise noted in a normal person, since this rise is due to the increase in amplitude of the x-wave which occurs with high-intensity stimuli. The lack of the photopic x-wave was also manifest in the low magnitude of the positive response of the color-blind subject at the beginning of dark adaptation and the absence of a "break" in the dark-adaptation curve which normally occurs when both photopic and scotopic processes are present.

The normal a-wave is assumed to consist of a photopic and a scotopic component.[12,14,21,22] This conclusion is based in part on the appearance of a "break" in the dark-adaptation curve of the a-wave and the different appearance of this wave in response to red and blue stimuli. The assumption of the dual nature of the a-wave is apparently supported by the fact that it often appears to be split into two portions, separated by a small positive "hump." According to the hypothesis of Armington, Johnson, and Riggs,[21] this phenomenon may be due to the existence of a photopic a-wave (a_1) and a scotopic a-wave (a_2) with different latencies. In the present study, such a temporal differentiation was disregarded intentionally, and the values for the a-wave refer to the over-all amplitude regardless of the appearance of "humps" in the wave. The temporal aspects of the a-wave, as studied in normal subjects and those with congenital retinal anomalies, will be discussed in a future publication.

The a-wave of the color-blind subject showed an intensity function similar to the normal, but greatly reduced in size. The amplitude at the commencement of dark adaptation was also below normal, and the progressive increase during the later stages showed no evidence of a "break." Therefore, the conclusion appears to be justified that the a-wave of the color-blind subject represents a pure scotopic component, as previously demonstrated for the positive response in this subject.

The a-wave of the night-blind subject was identical in its behavior with the normal a-wave in regard to both intensity function and course during dark adaptation. Repeated examinations in this subject invariably showed a very definite "break" in the dark-adaptation curve of the a-wave and a continued growth in amplitude of the wave beyond the first 10 minutes of dark adaptation. On the basis of this evidence it must be concluded that the a-wave in this night-blind subject revealed evidence of a functioning scotopic process.

The absence of the scotopic positive wave (b-wave) in the congenitally night-blind subject is consistent with the lack of scotopic activity noted on subjective testing. The preservation of the scotopic portion of the a-wave in this subject is evidence that the primary photochemical process in the scotopic system is intact. What explanation can be offered for these seemingly contradictory findings?

Granit [23] (1947) reviewed earlier work which indicated that the a-wave might arise in a more distal locus than the b-wave; the recent experiments of Noell [24] (1953) also support this idea. Noell suggested that the a-wave cannot develop without specific reaction at the linkage between the inner and outer limbs of the receptor, while the b-wave requires the participation of structures

proximal to the inner limbs. In terms of this hypothesis, the present findings in the congenitally night-blind subject could reflect a disturbance limited to the inner segments of the scotopic receptor-cell and/or to their connection with the bipolar cells. Thus, the intact peripheral portion of the receptor would generate the normal scotopic a-wave, but the block in transmission to more central structures would account for the absence of the scotopic positive wave and the lack of scotopic activity noted in subjective tests. This interpretation is necessarily a speculative one, since the site of generation of the electroretinographic waves is still unsettled and the morphological basis of the functional disturbance in the night-blind subject is unknown.

The electroretinographic response in the night-blind subject, consisting of a large a-wave, an x-wave, and complete absence of the scotopic b-wave, has been noted in two other reported cases of congenital night blindness.[15,16] François[25] recorded an x-wave, and an a-wave of normal size, in three congenitally night-blind subjects, as did Armington[16] in another case. Quantitative studies of the a-wave during the course of dark adaptation were not done in these six subjects; as a result, no conclusions can be drawn regarding the presence of a scotopic component in their tracings. In two other cases of night blindess (Armington[5] and Riggs[26]) a b-wave of reduced amplitude was found in addition to photopic components. The subjective findings in all reported subjects, however, were similar in that the scotopic portion of the dark-adaptation curve was absent. Therefore, despite the uniform findings in psychophysical tests of congenitally night-blind subjects, the dissimilar patterns of electroretinographic response suggest that there is more than one type of congenital night blindness. It may be that the defect in these cases involves different portions of the distal rod pathways.

The investigation of new cases of congenital night blindness is necessary to establish to what extent normal scotopic electroretinographic components may be found in the presence of marked deficiences of scotopic function on psychophysical testing. In the case of the totally color-blind, additional electroretinographic studies are also indicated, since the apparent agreement in the two reported cases does not preclude the possibility of different results in new subjects. In particular, it would be interesting to know whether any subjects with total color blindness exhibit a dissociation between the behavior of their positive and negative waves, in a manner analogous to that of the congenitally night-blind subject in this study.

Though new questions have been raised by the findings in the negative wave of the congenitally night-blind subject, the behavior of the positive wave in this subject, and both positive and negative waves in the color-blind subject, followed a pattern consistent with previous investigations. This supports the assumption that the electroretinogram, like other sources of data of visual function, may be studied as the resultant of photopic and scotopic activity.

Summary

A congenitally night-blind, a totally color-blind, and three normal subjects were studied electroretinographically with single-flash stimuli under identical conditions. The effect of increasing stimulus intensity and dark adaptation on the negative electroretinographic wave (a-wave) and positive wave (b-wave and/or x-wave) was investigated in each subject.

The negative and positive waves (a-wave and b-wave) of the totally color-blind subject reflected exclusively scotopic activity, and the positive wave (x-wave) of the congenitally night-blind subject reflected photopic activity. However, the negative wave (a-wave) of the night-blind subject demonstrated both scotopic and photopic activity, as in the normal subject.

The significance of these findings was discussed.

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REFERENCES

1. Hecht, S.; Shlaer, S.; Smith, E.; Haig, C., and Peskin, J. C.: The Visual Functions of the Complete Color Blind, J. Gen. Physiol. 31:459, 1948.

2. Hecht, S.: Rods, Cones, and the Chemical Basis of Vision, Physiol. Rev. 17:239, 1937.

3. Bornschein, H.; Goodman, G., and Gunkel, R. D.: Temporal Aspects of the Human Electroretinogram, A. M. A. Arch. Ophth. 57:386, 1957.

4. Riggs, L. A.; Berry, R. N., and Wayner, M.: Comparison of Electrical and Psychophysical Determinations of the Spectral Sensitivity of the Human Eye, J. Optic. Soc. America 39:427, 1949.

5. Armington, J. C.: Electrical Responses of the Light-Adapted Eye, J. Optic. Soc. America 43:450, 1953.

6. Johnson, E. P., and Cornsweet, T. N.: Electroretinal Photopic Sensitivity Curves, Nature, London 174:614, 1954.

7. Armington, J. C.: Amplitude of Response and Relative Spectral Sensitivity of the Human Electroretinogram, J. Optic. Soc. America 45: 1058, 1955.

8. Dodt, E.: Cone Electroretinography by Flicker, Nature, London 168:738, 1951.

9. Bornschein, H., and Schubert, G.: Das photopische Flimmer-Elektroretinogramm des Menschen, Ztschr. Biol. 106:229, 1953.

10. Dodt, E.: Ergebnisse der Flimmer-Elektroretinographie, Experientia 10:330, 1954.

11. Goodman, G., and Iser, G.: Physiological Studies with Flicker Electroretinography, Am. J. Ophth. 42:212 (Oct., Pt. 2) 1956.

12. Bornschein, H.: Der Einfluss von Adaptationszustand und Reizintensität auf die Komponenten des menschlichen Elektroretinogramms, Ztschr. Biol. 105:454, 1953.

13. Alpern, M., and Faris, J. J.: Note on the Electrical Response of the Human Eye During Dark Adaptation, J. Optic. Soc. America 44:74, 1954.

14. Auerbach, E., and Burian, H. M.: Studies on the Photopic-Scotopic Relationships in the Human Electroretinogram, Am. J. Ophth. 40:42 (Nov., Pt. 2) 1955.

15. Schubert, G., and Bornschein, H.: Beitrag zur Analyse des menschlichen Elektroretinogramms, Ophthalmologica 123:396, 1952.

16. Armington, J. C., and Schwab, G. J.: Electroretinogram in Nyctalopia, A. M. A. Arch. Ophth. 52:725, 1954.

17. Armington, J. C., and Thiede, F. C.: Selective Adaptation of Components of the Human Electroretinogram, J. Optic. Soc. America 44: 779, 1954.

18. Armington, J. C.: A Component of the Human Electroretinogram Associated with Red Color Vision, J. Optic. Soc. America 42:393, 1952.

19. Dodt, E., and Wadensten, L.: The Use of Flicker Electroretinography in the Human Eye, Acta ophth. 32:165, 1954.

20. Vukovich, V.: Das ERG des Achromaten, Ophthalmologica 124:354, 1952.

21. Armington, J. C.; Johnson, E. P., and Riggs, L. A.: The Scotopic a-Wave in the Electrical Response of the Human Retina, J. Physiol. 118:289, 1952.

22. Best, W.: Das menschliche Elektroretinogramm während der Dunkeladaptation, Acta ophth. 31:95, 1953.

23. Granit, R.: Sensory Mechanisms of the Retina, London, Oxford University Press, 1947.

24. Noell, W. K.: Studies on the Electrophysiology and the Metabolism of the Retina, Randolph Field, Texas, U. S. A. F. School of Aviation Medicine, 1953.

25. François, J.; Verriest, G.; De Rouck, A., and Dejean, C.: Les Fonctions visuelles dans l'héméralopie essentielle nougarienne, Ophthalmologica 132:244, 1956.

26. Riggs, L. A.: Electroretinography in Cases of Night Blindness, Am. J. Ophth. 38:70 (July, Pt. 2) 1954.

Retinitis Pigmentosa, Acanthrocytosis, and Heredodegenerative Neuromuscular Disease

ABRAHAM L. KORNZWEIG, M.D., and FRANK A. BASSEN, M.D., New York

In a previous report[1] we presented the case of a 17-year-old girl with an atypical type of retinitis pigmentosa, progressive neuropathy, and a hitherto undescribed abnormality of the red blood cells.

The parents of the girl were first cousins, and, as far as could be determined, normal in all respects. It was felt that the symptoms and signs in this patient represented a clinical entity of an hereditary nature, since the red cell abnormality was also present in a younger brother.

Shortly afterward, Singer et al.[2] reported a remarkably similar case and gave the descriptive term of acanthrocytes* to the abnormal red cells. The parents in this case were second cousins and also apparently normal in all respects.

In both cases there was an early history of celiac disease and the neurological changes were similar. In Singer's case, however, there were no retinal changes.

The patient to be reported is the brother of our first case. At the time he was first found to have abnormal red cells there were minimal ocular changes but no other noteworthy findings. However, the disease has progressed, and, in view of the rarity of this condition, we felt that this patient's case should be reported.

Report of Case

A white boy, born of Jewish parents, was first seen Feb. 13, 1948. He was then 9 years old. A past history at that time revealed that he was born at term and weighed 5¾ lb. (2610 gm.). Delivery was normal and noninstrumental. There was no jaundice or any other disease in the neonatal period. He developed celiac disease at the age of 9 months and recovered after one year of therapy. He sat up at 7 months, walked at 14 months, and started talking at 16 months. During childhood he had measles, mumps, pertussis, and chickenpox.

His parents were first cousins, and he was their third and youngest child. He had one normal sister and one sister who, at the time he was first seen, was 17 years old and had the clinical picture already referred to. There was no history of familial eye disease or neurological disease on either side of the family.

The patient, when first seen, had no complaints, either ocular or neurological. The vision was 20/25 in the right eye with a +1.00 cylinder at axis 115 degrees. The vision in the left eye was 20/20 with a +0.50 cylinder at axis 65 degrees. There was an exophoria under cover and poor convergence; the near point varied from 160 to 240 mm. The fundus examination showed a normal optic disc and macula, with normal retinal vessels. However, in the midperiphery pigmentary changes were noted. These consisted of areas of depigmentation and a few spots of pigmentary proliferation. An attempt was made to determine the peripheral fields, and, even though cooperation was poor, a definite but irregular constriction was noted in the right eye but there was practically none in the left eye (Fig. 1).

The boy was of moderate intelligence and was making good progress at school, and, because there were no obvious neurological signs or symptoms, no neurological examina-

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* Acanthous, spiny.

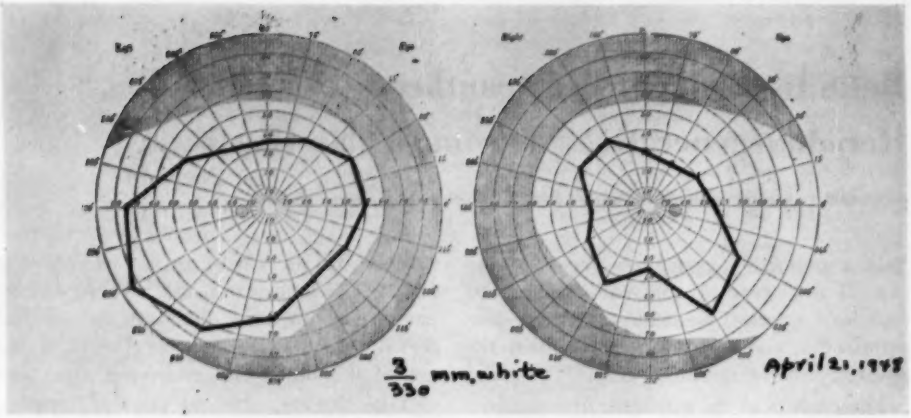


Fig. 1.—Peripheral fields of vision of patient at the age of 9 years. There is a partial contraction of the field for white in the right eye. The left eye appears normal.

tion was made at this time. Blood smears, however, were made of the whole family because of the unusual red blood cells found in his sister. Abnormal red cells were found in the patient's blood films. The count in general was normal except that it showed a slight anemia. Great numbers of the red cells, however, revealed unusual abnormalities in shape and to some extent in size (Fig. 2). In general, they had a crenated appearance but of such a degree that they took on bizarre shapes, simulating small beetles, crabs, and turtles. Others were star-shaped. Some of the cells resembled spherocytes from which buds or pseudopods were protruding. Detailed hematological studies were not made on this patient, but in the two previously reported cases detailed studies failed to reveal anything to explain the red cell abnormality. Singer suggested that it is due to a mutant recessive allele for a gene which controls the normal architecture of the red cell.

The patient was seen again in July, 1950. His vision with glasses was still very good —20/30 in each eye—but he had developed

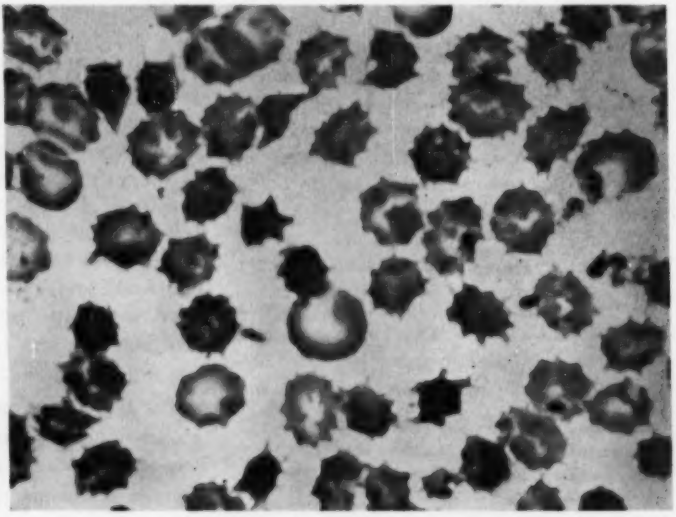


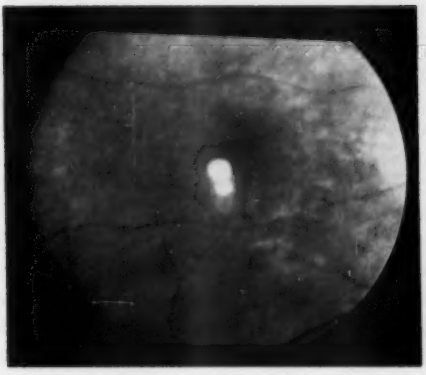
Fig. 2.—Appearance of the red blood cells on ordinary blood smear stained with Wright's stain. Note the generally crenated appearance of the red cells and the variations in size. The smaller, deeply stained cells resembling spherocytes undergoing crenation stand out sharply.

a right exotropia and fixed chiefly with his left eye. The fundus examination showed a more marked pigmentary degeneration of the retina. Neurological symptoms had begun to appear. He had trouble walking, and he would suddenly "flop" and fall to the ground. These episodes were momentary and recurred daily. He was clumsy in using his hands and had difficulty in catching a baseball. He stuttered when talking. His bladder appeared to be weak. When he laughed he wet his underclothing. There were spells of giggling.

A neurological examination was made by Dr. Morris Bender. His report disclosed numerous neurological and muscular disorders. There was inability to arise with ease from a reclining position. The gait was waddling and unsteady. There was marked lordosis and prominence of the abdomen. There was wasting of the muscles around the shoulder girdle and upper and lower extremities. There was weakness of the muscles of all extremities, trunk, and neck. All the deep reflexes were absent and could not be obtained with reenforcement. There was a positive Romberg sign. There was ataxia in the performance of the heel-to-knee test and some ataxia in the finger-to-nose test. Dysdiadochokinesia was evident in both hands. Vibration sense was very much diminished to absent in all four extremities. This was most marked distally and below the iliac crests. Position sense was impaired in the toes. There was glove-and-stocking type of hypesthesia. The speech was nasal. Hearing was slightly defective for high tones.

Dr. Bender's opinion was that the patient had an heredodegenerative neuromuscular disorder, with signs of diffuse myeloneuropathy and muscular dystrophy. The etiology appeared to be familial.

During the next few years the disease progressed both neurologically and ophthal-



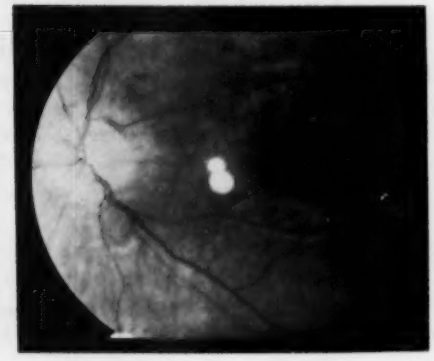


Fig. 3.—Fundus photographs of the right and left eyes showing the pallor of the disc and the marked narrowing of the retinal arteries. In the lower photograph a section of the midperiphery is seen, with a spot of pigmentary degeneration.

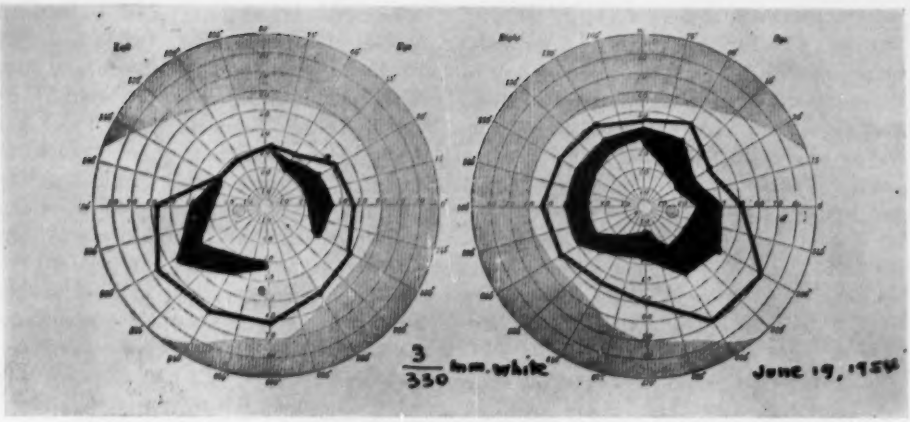


Fig. 4.—Peripheral fields at the age of 15 years, showing a complete ring scotoma in the right eye and a partial ring scotoma in the left eye.

mologically. The optic discs were paler, and the retinal vessels were narrowed. Pigmentary degeneration had advanced so that it was readily seen in midpheriphery (Fig. 3). The fields of vision showed a complete ring scotoma in the right eye and a partial ring scotoma in the left eye (Fig. 4). Vision with correction was still 20/30 in each eye, although the patient now had compound myopic astigmatism. He had been operated on for the right exotropia at Bethesda Hospital, Md. He now is incapable of going to school because of the ataxia and has to get instruction at home. His intelligence remains good.

The blood picture has remainded unchanged since the original observation. He still has the same peculiar type of red blood cells. This has been checked as recently as March 3, 1956, eight years after the original observation.

An electroretinographic examination of the entire family was done by Dr. Jerry Jacobson, at the New York Eye and Ear Infirmary, and revealed a complete absence of electrical response in the two affected children and a normal response in the parents and remaining child.

Comment

This is the third reported case of a rare hereditary disorder characterized in all three cases, so far, by early celiac disease, progressive ataxic neuropathy, and a peculiar malformation of the red blood cells. Two of the cases reported were brother and sister, and the parents were first cousins. In the third case the parents were second cousins; so it is believed that consanguinity plays an important role in the development of this unusual condition. The trait probably occurs recessively in certain families and manifests itself with consanguinity.

The development and course of the disorder have been remarkably similar in all cases, with the important exception, however, that there were no retinal changes in the case reported by Singer et al. In the brother and sister, retinitis pigmentosa occurred, without macular involvement in the boy and with macular degeneration in the girl.

The neurological signs and symptoms appeared rather late in all the cases, and Singer et al. considered the possibility that they were a sequelae of the celiac syndrome. However, we concur with their opinion that the neurological disorder probably belongs to the group of hereditary ataxias. The red cell abnormality, which is striking, evidently is an inherent part of the over-all picture. The case herein reported has not been studied in a detailed hematological fashion, but the red cell ab-

normality appeared identical to that of the other cases described. Detailed hematological studies were made in the two previously reported cases, but nothing was found that contributed to our understanding of the malformations of the red cells.

If reports of cases of this type are any indication of the prevalence of this disorder, it must be exceedingly uncommon. The prerequisites of consanguinity plus the presence of the traits in both parents could explain why this condition is so rarely seen. Whether other hereditary ataxic neuropathies, as mentioned by Portier and associates, with or without the hematological changes, are related, cannot be stated.[3] Close attention to the appearance of the blood smear in related cases of ataxia or retinitis pigmentosa may bring more cases to the fore.

Summary

Another case is reported of a child born of consanguinous parents who showed the development of a fairly typical retinitis pigmentosa, a diffuse heredodegenerative neuromuscular disorder, and a peculiar malformation of red blood cells, acanthrocytosis. The patient has been followed for eight years, during which time the neurological and ocular symptoms have progressed. The appearance of the red blood cells has remained unchanged during the period of observation.

1 E. 63d St. (21).

REFERENCES

1. Bassen, F. E., and Kornzweig, A. L.: Malformations of the Erythrocytes in a case of Atypical Retinitis Pigmentosa, Blood 5:381-387 (April) 1950.

2. Singer, K.; Fisher, B., and Perlstein, M.: Acanthrocytosis: A Genetic Erythrocyte Malformation, Blood 7:577-591 (June) 1952.

3. Portier, A.; Massonnat, J.; Garre, H., and Natter, S.: Nouvelle contributions à l'étude des syndromes neuro-hémolytiques, Semaine hôp. Paris 30:1632-1644 (April 22) 1954.

Riley-Day Syndrome (Familial Dysautonomia)

Concerning the Etiology of the Corneal Pathology; An Ocular Survey of Nineteen Cases

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It is the purpose of this communication to discuss the possible causes and treatments of the ocular manifestations of the Riley-Day syndrome. Children who have this disease invariably cry without tears and almost always have corneal hypesthesia or anesthesia, and some of them sleep with their eyes partially open, especially when they are acutely ill. Moreover, they are often subject to bouts of very high fever, vomiting, diarrhea, bronchopneumonia, profuse salivation, and sweating. Hereafter, for the purpose of convenience, these symptoms will be referred to as "dehydration symptoms." Furthermore, their food intake is often subnormal, and therefore they may well be candidates for vitamin and nutritional deficiencies.

In a recent paper, I [1] reported three cases representing three different types or degrees of corneal involvement in the Riley-Day syndrome.* The first case was that of severe ulceration and extensive opacification of the cornea, similar to the cases previously described by Dunnington.[6] The second case showed only a mild superficial disturbance in the corneal epithelium, without actual ulceration but with considerable turbidity of the corneal stroma. This lesion was located in the lower one-third of the cornea, in contrast to the first case, which was primarily central. The third case was discovered on routine examination of a child with known Riley-Day syndrome but with no previous history or symptoms of ocular involvement. The cornea in this case showed only faint scarring inferiorly, just within the limbus, having the appearance of etched glass, and this scarring was detected only with the aid of a magnifying device. The variation in the severity of corneal involvement in these three patients prompted the present survey. It was hoped that such a study might elucidate etiologic factors and provide suggestions for their prevention and treatment. From the symptoms referred to above, the following factors might be expected to play a role: (*a*) neurotrophic factors, as in neuroparalytic keratitis; (*b*) exposure; (*c*) dehydration; (*d*) vitamin A deficiency.

The present survey includes 19 patients who were from 1½ to 17 years of age. These children are all of Jewish extraction, and there is no sex predominance. The principal findings are summarized in the accompanying chart. They are arranged in the order in which they came to my attention. The first three patients are described briefly above and have been presented recently in greater detail.[1] Patients 4 to 18 were examined in New York with the permission of Dr. Conrad Riley, who also provided me with such details of the medical history as are herein recorded. Patient 14 was reported in detail by Dunnington [6] as his Case 1. Case 19 has not been completely accepted as having the Riley-Day syndrome. Wherever possible, the corneas were examined with the slit-lamp microscope. A few children were too young and too uncooperative for this procedure, and these were examined with the Zeiss loupe

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From the Children's Medical Center, Massachusetts Eye and Ear Infirmary, and Department of Ophthalmology, Harvard Medical School.

* A complete description of the syndrome can be found in a series of articles by Riley et al.[2-5]

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Age when examined *(years)*	2	6	$3\frac{1}{2}$	$5\frac{1}{2}$	3	17	2	$5\frac{3}{4}$	9	$1\frac{1}{2}$	2	$5\frac{1}{2}$	3	$12\frac{1}{2}$	13	13	15	$1\frac{3}{4}$	$1\frac{1}{2}$
Sex	M	F	M	F	F	F	F	M	F	F	M	F	F	M	M	M	F	F	M
"Dehydration symptoms"	+++	++++	+++	++	+++	+++	+++	0	++++	±	+++	+++	+++	++++	++++	±	+++	+	++
Corneal hypesthesia	+++	+++	+++	+++	?	+++ in early life, now slight + OD and some OS	?	OD ++ OS ++++	+++	++	?	++	++	+++ in early life, now only slight	0	+++	0	?	+++
History of exposure of corneas in sleep	+++	++	+	+++	+++	0	0	Always a little — more when ill	+++	0	0	0	0	0	0	+	0	0	+
Defective lacrimation	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Corneal scarring	Deep, diffuse keratitis OU Severe	Superficial and deep moderate-severe	Superficial punctate lower $\frac{1}{3}$ minimal	Superficial OU lower $\frac{1}{3}$ minimal	Slight OS only	OS only	Neg.	OD + OS	Superficial and deep Ind. severe Homogeneous hazy scar Nodule OS	Neg.	Neg.	Neg.	Neg.	Deep exposed areas Severe	Neg.	Deep Severe Dense central vascularized	Neg.	Neg.	Neg.

and flashlight. Corneal sensitivity was tested with a cotton wisp. The following points are of particular interest:

1. Ten of the nineteen patients showed corneal pathology.

2. Analysis of these 10 patients shows that (*a*) 8 of the 10 had corneal hypesthesia or anesthesia. Of the two that did not, one (Case 5) was too young for adequate testing and the other (Case 6) is reported to have had corneal hypesthesia in childhood and seems to have acquired corneal sensation as she grew older. Even in this girl, there seems to be slight hypesthesia in the right eye. However, this patient's right eye showed no pathology, and such scarring as was seen was in the left eye, where sensation was found to be normal!

(*b*) Although 8 of the 10 children with corneal pathology had bouts of fever, vomiting, perspiration, and dehydration, two did not (Cases 8 and 16).

(*c*) Three had the severe neuroparalytic type of keratitis involving primarily the central portions of the cornea (Cases 1, 14, and 16). All three required lid suturing to arrest the ulcerative process.

(*d*) In the seven mild cases there was minimal, irregular scarring in the lower one-fourth to one-third of the cornea—that portion which might be exposed in sleep. Every child who was known to sleep with his eyes open showed corneal scarring (except one, Case 19, and this patient may not actually have the syndrome). Almost every child who had corneal scarring was known to sleep with his lids partially separated except for two, Cases 6 and 14, where there was definite corneal involvement with a negative history for this exposure factor.

(*e*) In five patients there was no history nor had there been any symptoms of ocular disease. The ocular involvement was discovered for the first time in the course of this survey and consisted only of faint scarring within the lower limbus.

3. In eight cases there was no corneal pathology and analysis of these cases showed that: (*a*) six had definite dehydration symptoms, some of them severe. One of these patients (Case 12) also had corneal hypesthesia. Her mother states that this child was subject to seizures when she was younger and was observed to sleep with her eyes open. The mother states that, as soon as she noted this, she attended the child constantly when she was very ill and manually closed her lids.

(*b*) Four were children 3 years old or younger. I was unable to draw any definite conclusions as to their corneal sensitivity to touch, but it is most probable that eventually they will be found to have corneal hypesthesia, since this is an almost constant finding in this syndrome. Their failure to show corneal pathology may be due to the fact that they are so young, and if they are reexamined at a later date some of them may show corneal involvement. It is possible that these four children may be too young to have had enough exposure. Finally, they may merely have a mild form of the syndrome.

4. In every case, the history and examination showed that the child cried without tears. However, many parents volunteered the information that the eyes were not absolutely dry and one could often see "a tear standing in the eye."

5. Two patients, Cases 6 and 14, who are 17 and 12½ years old, respectively, showed definite corneal hypesthesia in early life but have only very slight or no hypesthesia now. This suggests that the neurologic disturbance in familial dysautonomia may diminish with the passage of time. Perhaps this accounts for the fact that active corneal ulceration has not been found in children over 8 years old.[2-5]

Comment

It is apparent that "dehydration symptoms" alone are not responsible for the corneal pathology, since six children with severe dehydration symptoms had no keratopathy and two with severe corneal involvement had no dehydration symptoms. Corneal hypesthesia and lack of tearing are the constant findings. Exposure during sleep and dehydration may be of some importance, but they are not constantly present.

There are good reasons to think that we are dealing with a form of neuroparalytic keratitis. Kroop[7] has shown that 3 mg. of methacholine (Mecholyl) chloride injected subcutaneously will produce tearing in children with Riley-Day syndrome, and this suggests that the lacrimal gland must be normal and the fault must lie in its innervation. According to Berliner,[8,9] neuroparalytic keratitis follows a disturbance of the trigeminal nerve supply to the cornea and the site of the lesion may be ganglionic, infraganglionic, or supraganglionic. There may be slight epithelial edema or severe exfoliative destruction of the epithelium, ulceration, and even necrosis of the entire cornea. Of course, there is corneal anesthesia, and the indolent keratitis has often been attributed to trophic interference with normal epithelial cellular metabolism. According to Adler,[10] the function of tearing is innervated by the lacrimal branch of the fifth nerve, the sympathetic nerve, and the great superficial petrosal nerve (derived from the facial). The following clinical observations are therefore appropriate:

1. Total ablation of the Gasserian ganglion or transection of the sensory root of the trigeminal nerve does not produce a reduction in tear formation and does not necessarily result in a keratitis, when the ganglion is approached intradurally and the greater superficial petrosal nerve is spared, according to Dandy.[12]

2. A defect in the sympathetic innervation to the eye, as in Horner's syndrome, is not known to produce either keratitis or defective lacrimation. Mutch[13] stated that no interference with weeping occurs with unilateral or bilateral section of the cervical sympathetic.

3. Surgical transection of the great superficial petrosal nerve alone is said by Johnson[14] to produce a dry eye but not keratitis.

Verhoeff[15] therefore suggests that the *sine qua non* for neuroparalytic keratitis is damage to both the sensory root of the fifth cranial nerve and the great superficial petrosal nerve. This denervates the lacrimal gland and results in a dry anesthetic eye.

Similar reasoning might be applied to the keratitis of familial dysautonomia; however, it is difficult to be certain of the exact nature and localization of lesions produced

by neurosurgical procedures without detailed postmortem pathologic studies. Moreover, since there is marked diminution in both psychic and reflex tearing in this syndrome, a supranuclear lesion would be more likely than a peripheral one. Also, because of the widespread nature of the systemic signs and symptoms, Riley [2-5] considers that the defect is probably central rather than peripheral.

Segall [17] described two children who cried without tears and had bilateral corneal pathology similar to that of Dunnington's cases and my Case 1 as having "congenital neuroparalytic keratitis." His cases had multiple developmental anomalies. Walsh [18] stated that he had had no experience with neuroparalytic keratitis in congenital paralysis of the fifth nerve.

Concerning exposure keratitis, Berliner [8, 9] says, "Exposure keratitis is associated with orbicularis oculi paralysis induced by affections of the facial nerve, or with faulty closure of the eyelid in exophthalmos, ectropion, eyelid cicatrices, and coma. The imperfect closure of the eyelids leaves the mucous surfaces in prolonged contact with the air and results in overevaporation of the tear fluid with consequent desiccation of the epithelium. Degeneration of the epithelium is followed by xerosis. The early biomicroscopic picture usually seen is that of a delicate, punctate epithelial haziness, *appearing especially in the lower parts of the cornea* as a horizontal band of epithelial edema with eventual fissuring and exfoliation of the epithelium." Without question, the milder cases herein described resemble exposure keratitis. There is certainly some, but not complete, correlation between the exposure of the corneas in sleep and the incidence of corneal scarring in my series.

The question of vitamin A deficiency is an important one, for these eyes frequently show the absence of redness and the lackluster of the corneal epithelium so characteristic of keratomalacia due to vitamin A deficiency. In the past, cystic fibrosis of the pancreas was associated with vitamin A deficiency. In recent years, clinical vitamin A deficiency has not been seen in children with cystic fibrosis of the pancreas,[19] in all probability owing to the almost universal administration of watermiscible vitamin A. In a number of instances, children with Riley-Day syndrome were seriously considered to have cystic fibrosis, because these conditions have many features in common, such as chronic respiratory infection, failure to thrive, diarrhea, etc. In my Case 1 there was no clinical evidence of vitamin A deficiency (vitamin-A-absorption curves and dermatologic consultation). The autopsy showed no evidence of pancreatic fibrosis.

Congenital alacrimia is the absence of the secretion of tears persisting beyond the first few years of life. It can occur in otherwise healthy infants. Sjogren [20] described this in persons who later developed keratoconjunctivitis sicca (with or without associated nerve palsies). As a symptom, it is, of course, also present in the Riley-Day syndrome.

While the corneal pathology, especially in its mild form, is not necessarily diagnostic, its presence in a poorly-developing infant should suggest the possibility of familial dysautonomia.

Ophthalmologic Management

Since hypesthesia, defective lacrimation, and exposure seem to be the common denominators in the various types of involvement, treatment should be directed toward minimizing these three factors. Liberal instillations of a tear substitute (0.33% methylcellulose) by day and a bland ointment (petrolatum) at night are indicated. These simple measures should be carried out whenever there is any suggestion of corneal pathology. An antibiotic can be used locally to prevent or combat secondary infection. Sealing the upper and lower puncta to conserve whatever moisture is present may be indicated in certain cases.

If the response to these conservative measures is not prompt, early protection of the cornea by a conjunctival flap or lid

adhesion should not be delayed. The severe neuroparalytic type of corneal involvement may proceed extremely rapidly. Belated surgical treatment may arrest the process, but dense extensive scarring with marked visual loss may result.

Inasmuch as the eyes of these patients are anesthetic in varying degrees, the hazards of undetected foreign bodies or corneal abrasions are obvious. It is most important, therefore, to avoid these injuries wherever possible and to secure prompt treatment when they occur.

Summary

A survey of 19 patients with the Riley-Day syndrome has been made, with emphasis on possible factors contributing to the etiology of the ocular lesions. Ten of the nineteen patients showed some corneal pathology. Of these, three were of the severe neuroparalytic keratitis variety and seven showed minimal superficial scarring in the lower one-third of the cornea, more suggestive of exposure keratitis. There were two patients with corneal involvement who had none of the "dehydration symptoms." Apparently, fifth nerve weakness, with corneal anesthesia, diminished lacrimation, and possible "trophic disturbances," is fundamental to the development of the lesion. Exposure of the corneas in sleep and "dehydration symptoms" may play a secondary role. Treatment should be directed toward minimizing these various factors by the instillation of 0.33% methylcellulose drops in the daytime and a bland ointment at night. In very severe cases, tarsorrhaphy may be urgently required.

Drs. William Berenberg, Conrad Riley, Harry Shwachman, and Frederick Verhoeff gave assistance in the preparation of this communication.

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REFERENCES

1. Liebman, S. D.: Ocular Manifestations of Riley-Day Syndrome: Familial Autonomic Dysfunction, A. M. A. Arch. Ophth. 56:719, 1956.

2. Riley, C. M.; Day, R. L.; Greeley, D. M., and Langford, W. S.: Central Autonomic Dysfunction with Defective Lacrimation: Report of 5 Cases, Pediatrics 3:468, 1949.

3. Riley, C. M.: Familial Autonomic Dysfunction, J. A. M. A. 149:1532, 1952.

4. Riley, C. M.; Freedman, A. M., and Langford, W. S.: Further Observations on Familial Dysautonomia, Pediatrics 14:475, 1954.

5. Riley, C. M.: Living with a Child with Familial Dysautonomia, New York, The Dysautonomia Association, Inc., 1956.

6. Dunnington, J. H.: Congenital Alacrima in Familial Autonomic Dysfunction, A. M. A. Arch. Ophth. 52:925, 1954.

7. Kroop, I.: The Production of Tears in Familial Dysautonomia: Preliminary Report, J. Pediat. 48:328, 1956.

8. Berliner, M. L.: Biomicroscopy of the Eye, New York, Paul B. Hoeber, Inc., 1943, Vol. 1, p. 488.

9. Berliner, M. L.: Biomicroscopy of the Eye, New York, Paul B. Hoeber, Inc., 1943, Vol. 1, p. 471.

10. Adler, F. H., cited by Walsh.[18]

11. Duke-Elder, S.: Text Book of Ophthalmology: Vol. 5. The Ocular Adnexa, St. Louis, The C. V. Mosby Company, 1952, p. 5212.

12. Dandy, W., cited by Duke-Elder.[11]

13. Mutch, J. R., cited by Duke-Elder.[11]

14. Johnson, L. V., and Nosik, W. A.: Greater Superficial Petrosal Neurectomy for Relief of Chronic Bullous Keratitis, A. M. A. Arch. Ophth. 45:32, 1951.

15. Verhoeff, F.: The Cause of Keratitis After Gasserian Ganglion Operations, Am. J. Ophth. 8:273, 1925.

16. Verhoeff, F.: Personal communications to the author.

17. Segall, W.: Congenital Neuroparalytic Keratitis, Am. J. Ophth. 39:732, 1955.

18. Walsh, F.: Clinical Neurophthalmology, Baltimore, Williams & Wilkins Company, 1947, p. 1337.

19. Shwachman, H.: Personal communications to the author.

20. Sjogren, H.: Congenital Alacrimia and Keratoconjunctivitis Sicca in Children, Tr. Ophth. Soc. New Zealand, p. 32, 1952.

The Toxic Effect of Sodium L-Glutamate on the Inner Layers of the Retina

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L-Glutamic acid and its sodium salt have been widely used in the oral treatment of petit mal and mental deficiency (e. g., Zimmerman, Burgemeister, and Putnam, 1949; Milliken and Standen, 1951). Single doses of 20-30 gm. have also been administered intravenously without permanent ill-effects (Sapirstein, 1943; Elman, 1946; Mayer-Gross and Walker, 1949; Weil-Malherbe, 1949).

During an investigation of the influence of various substances of biochemical importance upon the progress in the mouse of an hereditary retinal dystrophy it was observed that the parenteral administration of sodium L-glutamate damaged the inner layers of the retina, which are not themselves involved in the genetic lesion. Since this lesion could also be produced in normal mice, a limited study was made of its histological development and the conditions necessary for its appearance in mouselings and adults of the Strong A2 (Glaxo) strain. Among substances related chemically or physiologically to glutamate, which were also tested, only sodium L-aspartate had a similar effect.

Methods and Materials

Animals.—All work was performed on an inbred colony of Strong A2 (Glaxo) mice, fed throughout on rat cake Diet 41 (Bruce and Parkes, 1949). Adult mice used weighed 15-36 gm.; suckling mice, from litters of five to eight animals, when destroyed for histological purposes at 17 days, weighed 5-7 gm.

Substances Administered.—These consisted of (1) L-glutamic acid; (2) L-glutamic acid, sodium salt monohydrate; (3) α-ketoglutaric acid, sodium salt; (4) L-aspartic acid, sodium salt; (5) L-glutamine; (6) ammonium carbonate; (7) epinephrine hydrochloride solution, 0.1% (w/v); (8) adenosinetriphosphate, sodium salt (ATP); (9) methanol; (10) quinine dihydrochloride, solution 20% (w/v); (11) 2,4-dinitrophenol, sodium salt.

The materials were made up in 0.85% saline or Krebs-Ringer solution and brought to pH 7.4 with phosphate buffer. Concentrations were adjusted to give injection volumes of 0.01-0.20 ml. in the mouselings and 0.5-1.2 ml. in the adults. Administration was subcutaneous unless otherwise specified.

Treatment.—To produce a severe retinal lesion by a single injection, a dosage of glutamate a little less than lethal was needed. This method proved suitable in the adult, but a course of injections at a lower level in the suckling mouse gave the same result with fewer casualties. A similar system of dosage was used in testing the other compounds upon adult and young mice. The latter were particularly liable to overdosage during their first 10 days of life and hence usually received during this period a smaller dosage (milligrams per gram of body weight) than that administered between 11 and 17 days.

Administration During Growth (Table 1).—(1) Glutamate: (*a*) To test the possibility that sodium glutamate might reach the fetus or suckling in effective quantity

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TABLE 1.—*Dosage of Substances Given Daily to Mouselings Aged Two to Sixteen Days*

	Substances, Mg./Gm. Body Weight				
	Sodium L-Glutamate	Sodium L-Aspartate	L-Glutamine *	Epinephrine	Ammonium Carbonate
Age, days, & weight, † gm.					
2 (1.80)	2.20	0.50	1.10	0.004	0.20
6 (3.28)	3.70	0.90	2.30	0.006	0.20
10 (4.36)	4.60	0.96	3.20	0.012	0.20
13 (5.43)	4.80	1.00	3.20	0.014	0.20
16 (5.56)	5.40	1.30	3.00	0.014	0.20
Total dose,‡ mg.	240	45	125	0.40	8.3
Animals					
No. used	70	14	7	19	11
Survivors for hist. study, No.	39	5	7	10	5
Age when killed, days	2–40	17	17	17	17

* Dose given in two equal portions, six hours apart.
† Mean value based on five litters comprising 27 mouselings.
‡ Typical total dose given between 2 and 16 days.

from the mother adult females received this substance parenterally, in doses of 40 mg. per day, throughout gestation, lactation, or both; the 40 mouselings which were born received no special treatment but were examined at birth or 17 days later.

(*b*) For study of the lesion at various stages of development, some 70 mouselings were treated daily with sodium glutamate, according to the dosage schedule shown (Table 1); the 39 survivors were examined at ages of between 2 and 40 days. All were treated from 2 to 17 days, except 5 which were treated from 2 to 11 days and 4 which were treated from 11 to 17 days; these 9 were all examined at 17 days. The dosage schedule in Table 1 corresponds to a daily increment of 1.5-2.0 mg. sodium glutamate. Typical doses (in milligrams) given at various ages (days, in parentheses) were as follows: 2 (4); 12 (6); 20 (10); 26 (13); 30 (16).

(2) Other Substances: Particulars of dosage used of sodium aspartate, glutamine, epinephrine, and ammonium carbonate are given in Table 1.

Administration in Adult Life.—Details of the animals treated with glutamate and other substances are given in Table 2.

Histological Processing.—All the eyes were fixed intact in acid Zenker's fluid. After they were embedded in paraffin wax, sections were cut at 5μ to 6μ. Routine staining was with Erhlich's hematoxylin and eosin Y method; a few sections were also

TABLE 2.—*Dosage of Substances Administered to Adult Mice*

Substance	Route *	Dosage,† Mg./Gm. Body Wt.	Mice, No.	Survivors Examined Histologically	
				Mice, No.	Time After Last Dose, Days
Sodium L-glutamate	SC	4.0	3	3	
		6.0	9	7	1 hr.–21 days
		8.0	12	7	
		10.0	3	–	
		3.0 – 4.0 ‡	8	8	28
		1.0 – 1.5 §	6	6	1–10
Adenosinetriphosphate, sodium salt	IP	0.5**	6	1	10
		2.0	5	5	11
Sodium α-ketoglutarate	SC	5.2 – 6.8	5	3	10
Ammonium carbonate	IP	0.31	3¶	3	10
Dinitrophenol, sodium salt	IP	0.0165	4	4	11
Methanol	SC	8.0–10.0	15	5	3–11
Quinine dihydrochloride	SC	0.35#	8	6	3–11

* SC, subcutaneous; IP, intraperitoneal.
† Animals received single doses unless otherwise stated.
‡ Four received 12 doses and four received 24 doses on successive days.
§ These animals were mothers of litters mentioned in Table 1 and received 30–120 doses.
** Three doses were given, one hour before, one hour after, and simultaneously with a single injection (SC) of sodium L-glutamate, 8.0 mg/gm.
¶ These mice simultaneously received a single injection (SC) of sodium L-glutamate 4.0 mg/gm.
# Dosage based on Hunt (1904).

stained with Mallory's phosphotungstic acid and hematoxylin method.

Results

Suckling Mice.—(1) Effect of Sodium L-Glutamate: At birth the newborn mouse retina consists of a layer of ovoid nuclei some 65μ thick separated from two to three rows of ganglion-cell precursors by the inner fiber layer, which is some 12μ thick. By about six days after birth the ganglion cells have formed a single even row of cells. As seen in section, ganglion cells appear to vary considerably in size; in the adult, their nuclei range from 4μ to 8μ in diameter. From birth the cytoplasm of the ganglion cells is strongly basophilic.

While the ganglion-cell layer is differentiating, the inner nuclear layer becomes separated from the outer nuclear layer and the inner fiber layer increases rapidly in thickness until, by 17 days after birth, it is 30μ thick. Mitotic figures are not seen in the differentiating inner nuclear layer. The inner nuclear layer can be distinguished from the outer layer from about six days after birth in the area centralis, and the two layers are completely separated at about eight days.

Treatment of the mother alone with glutamate, either orally or parenterally, during gestation and lactation had no demonstrable effect on the retina at birth or subsequently, but treatment of the suckling mice themselves regularly resulted in severe retinal damage. Mice aged 2 to 4 days which were examined a few hours after injection on those days, showed pycnotic nuclei along the inner border of the future inner nuclear layer. Numbers of ganglion-cell nuclei were pycnotic or showed rather pale staining of the nuclear chromatin network, and there was concomitant cytoplasmic shrinkage and loss of normal basophilic staining. In the 4-day-old mice these changes were conspicuous (Fig. 2). By six to eight days after birth, the number of ganglion cells was substantially reduced and the inner nuclear layer was only half of its normal thickness at this age. The inner fiber layer, instead of growing, disappeared altogether by 8 to 10 days after birth. The remaining inner layer and ganglion cells gradually diminished, until by 17 days after birth only occasional cells remained. The outer nuclear layer was little affected, and differentiation of the visual cells proceeded almost normally, although the final number of rows of nuclei appeared slightly reduced. The only abnormality noted was the occasional eruption of groups of visual-cell nuclei through the outer limiting membrane to form mushroom-like protuberances among the rods themselves. This disturbance was first noted 10 days after birth and was sometimes severe enough to produce an appearance of arcading (Fig. 6), but the pigmented epithelium was never involved as in arcading due to chorioretinitis.

The optic nerve appeared much thinner in hematoxylin-and-eosin-stained sections in the treated animals than in the controls.

The mice treated up to 11 days after birth showed a similar picture, but a few more inner-layer and ganglion cells were preserved. The four survivors treated from 11 to 16 days after birth showed a still less severe picture. The inner layer was half its normal thickness, and numbers of recognizable ganglion cells were present. The outer nuclear layer was unaffected in both these groups treated over short periods.

Both litters and mothers withstood the routine treatment fairly well, though showing nervousness and tremor soon after injection. Larger doses (8-10 mg/gm.) often produced convulsions followed by a state of prostration, a finding similar to that of Goodman, Swinyard, and Toman (1946), who observed that a dosage of 8 mg/gm. given intraperitoneally to cats caused hyperpnea, seizures, and death.

(2) Effect of Other Substances Tested: Sodium L-aspartate. Three of the five animals receiving aspartate showed minimal lesions at the periphery of the retina. These lesions appeared to be identical in nature with the glutamate-induced lesion, although

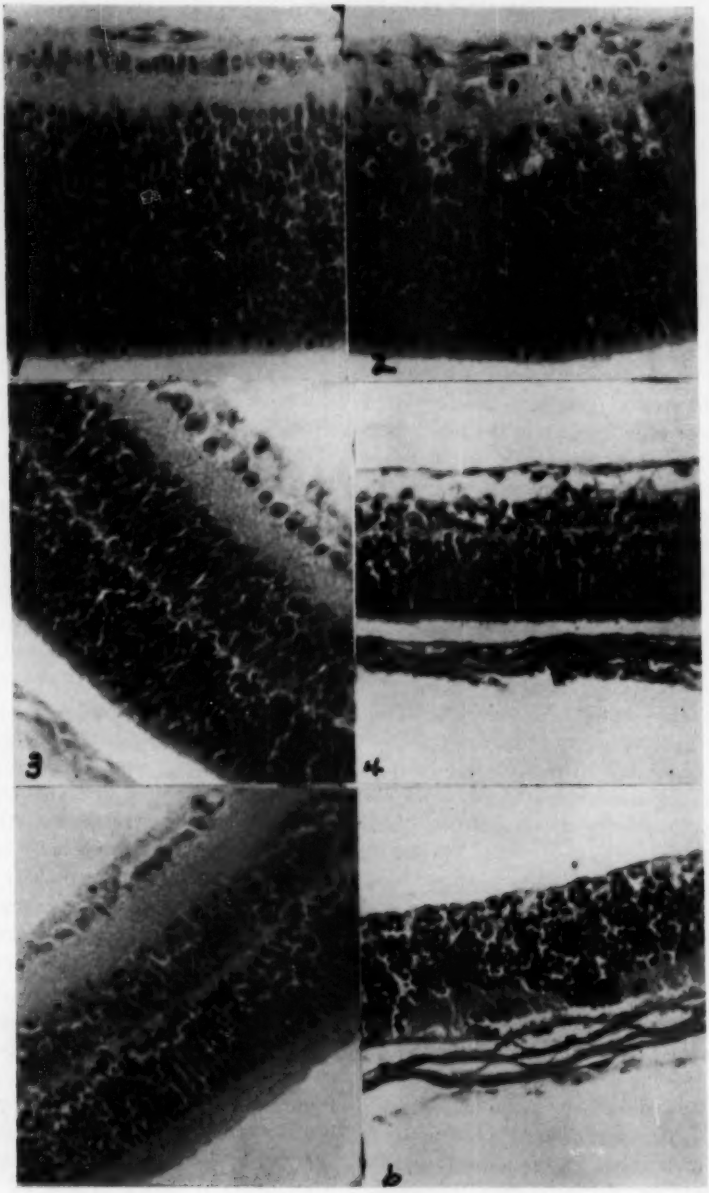

Plate I

Fig. 1.—Normal mouse retina four days after birth; × 290. All sections were stained with hematoxylin and eosin.

Fig. 2.—Retina of 4-day-old mouse after injections of 4 and 8 mg. of sodium glutamate on the second and fourth days, showing pycnotic nuclei in inner border and among ganglion cells; × 290.

Fig. 3.—Normal mouse retina eight days after birth; × 290.

Fig. 4.—Retina of 8-day-old mouse after daily injections of sodium glutamate, showing severe damage to the inner layers; × 290.

Fig. 5.—Normal mouse retina 17 days after birth; × 290.

Fig. 6.—Retina of 17-day-old mouse after daily injections of sodium glutamate, showing survival of only the outer nuclear layer with irregular protrusions of visual cells through the outer limiting membrane; × 290.

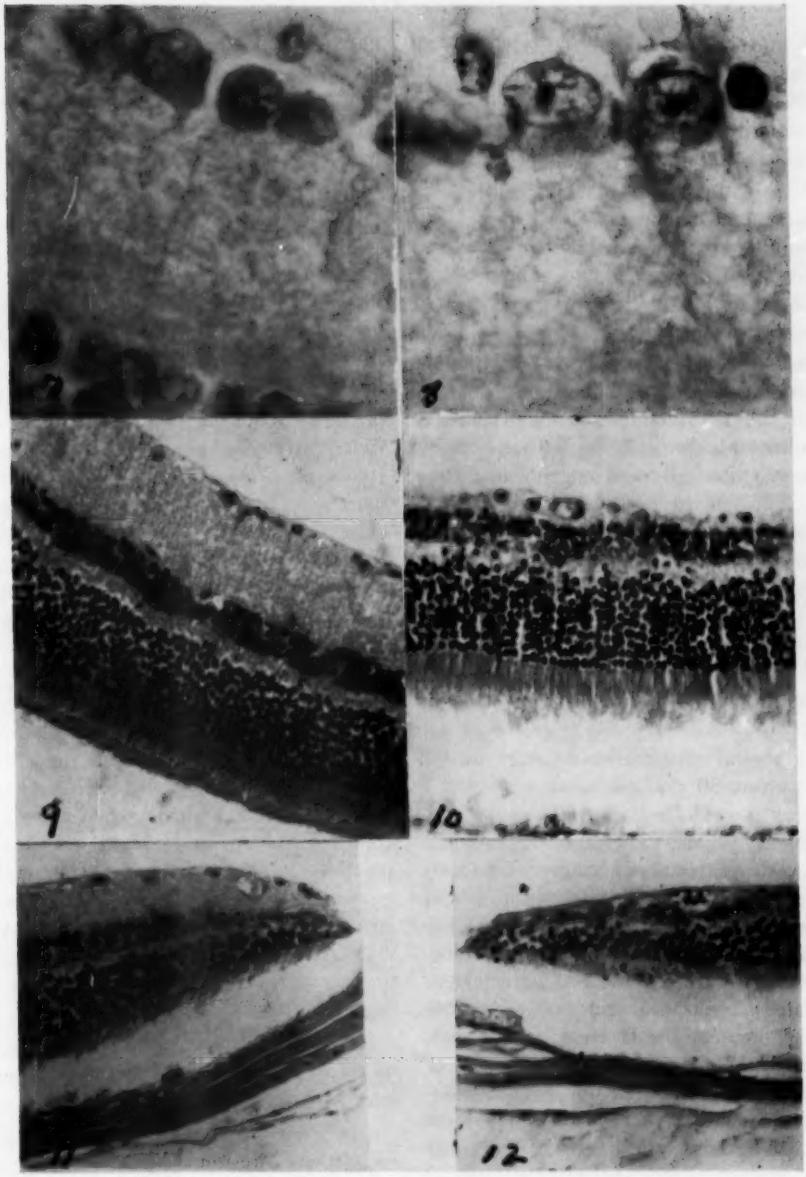

Plate II

Fig. 7.—Group of normal adult retinal ganglion cells; × 1000.

Fig. 8.—Group of adult retinal ganglion cells one hour after injection of 8 mg/gm. of sodium glutamate; two show chromatolysis and one has a pycnotic nucleus; × 1000.

Fig. 9.—Adult retina one day after injection of 8 mg/gm. of sodium glutamate, showing pycnotic nuclei in the ganglion-cell layer and inner nuclear layer and vacuolation of the inner fiber layer; × 290.

Fig. 10.—Adult retina 12 days after injection of 8 mg/gm. of sodium glutamate, showing severe destruction of the inner fiber layer and ganglion cells; × 290.

Fig. 11.—Ora serrata of normal adult; × 290.

Fig. 12.—Ora serrata 15 days after single injection of 6.0 ms/gm. of sodium glutamate (area centralis of this mouse was unaffected); × 290.

much more limited in extent. The remaining two animals showed no definite retinal abnormality.

Glutamine and epinephrine. None of the animals receiving these substances showed any demonstrable retinal abnormality.

Ammonium carbonate. This material was poorly tolerated; the animals tended to lose weight under treatment and to die before 17 days. None of the survivors showed any retinal abnormality.

Adult Mice.—(1) Effects of Sodium L-Glutamate: As in the suckling mice, the effect of sodium glutamate on the retina was manifested histologically as partial necrosis of the ganglion cells and inner-nuclear-layer cells. The periphery of the retina was regularly affected, but the central area sometimes escaped damage. The cells of the internal surface of the inner nuclear layer were more susceptible than those of the external surface. Even in the severely affected animals, complete destruction of the inner nuclear layer, as seen in the sucklings, did not occur.

Pathological changes were seen in the mouse killed 30 minutes after receiving 8 mg/gm.; in one, killed after 60 minutes, and in another, which died after 55 minutes, there were well-marked changes. The early changes seen were nuclear pycnosis both of the inner-layer and ganglion cells; the latter also showed loss of cytoplasmic staining. The inner fiber layer lost its characteristic reticulated appearance and became vacuolated. The outer fiber layer showed similar, but less well-marked, changes. Little change occurred during the next few days, but between 5 and 10 days after injection most of the necrotic tissue disappeared; there was no evidence of phagocytic removal such as occurs in the rabbit retina after destruction of the outer nuclear layer by iodoacetic acid (Karli, 1954).

The optic nerve was not systematically studied, but in several severely affected animals examined 12 to 15 days after receiving 8 mg/gm. of sodium glutamate, the fiber bundles in the papilla were found to be narrowed and the number of glial cells was increased.

The lesions produced by repeated doses do not require separate description, since they did not differ from the appearance found two to three weeks after a single injection.

The mouse surviving simultaneous treatment with sodium glutamate and ATP showed a severe retinal lesion identical with that seen after glutamate alone. Control animals receiving ATP alone were unaffected.

The histological changes varied rather widely at any given dosage level. The survivors of single doses of different magnitude have been classified into three grades of severity in Table 3. In the least severely affected, the lesion was so slight as to be only just recognizable at the ora serrata. In the severely affected, the damage involved the area centralis. The remaining grade was of intermediate severity.

The effects of the repeated doses cannot be compared accurately, since the dosage was not adjusted to body weight during the period of treatment. However, the weights of the animals when killed were recorded; so an approximate calculation is possible. Only one of the four animals receiving 12 doses of 100 mg. showed a lesion of moderate severity, but all the animals receiving 24 doses of 100 mg. (3.0 to 4.0 mg/gm.) were affected to a mild degree.

None of the mice which received a dose of 40 mg. (1.0 to 1.5 mg/gm.) daily over long periods was affected.

TABLE 3.—*Results of Single Doses of Sodium L-Glutamate in Adult Mice*

Dosage, Mg./Gm.	Animals, No.			
	Not Affected	Severity of Lesion*		
		+	++	+++
4	1	2	0	0
6	2	3	1	1
8	0	0	3	5

* +, The slightest detectable lesion; ++, lesion confined to the periphery; +++, lesion involving area centralis.

The mice treated with sodium glutamate and ammonium carbonate showed no retinal abnormality.

(2) Other Substances: The survivors in Table 2, after treatment with sodium α-ketoglutarate, quinine, or methanol, showed no histological abnormality.

Comment

The toxic action of sodium L-glutamate upon the retina does not appear to have been previously reported. The effect develops rapidly: Typical changes appear in the ganglion cells and inner nuclear layer of the mouse retina within 30 minutes after injection. Sublethal dosage is required to produce a lesion of consistent severity. The developing tissue (age 2 to 10 days) seems more sensitive than that of the older mouse.

Other agents reputed to produce comparable retinal lesions in various mammals proved ineffective when given in maximal dosage to the adult mouse. Methanol is reputed to damage the ganglion cells and optic nerves of mice (Weese, 1928; Harada, 1937), but the validity of these findings has recently been questioned by Gilger and Potts (1955) on technical grounds. While quinine appears to cause a similar lesion in the cat, dog, and rabbit (Holden, 1898; Birch-Hirschfeld, 1900; Druault, 1902), the present negative findings agree with those reported by Druault in the mouse.

The inner layers of the retina in structure resemble cerebral tissue, in which the functions of glutamate have been studied intensively. Though both tissues readily absorp glutamate from a glucose-saline medium (Stern, Eggleston, Hems, and Krebs, 1949), the content of this constituent is closely regulated in the brain of the intact animal. Schwerin, Bessman, and Waelsch (1950) and other investigators have shown that a dosage of sodium L-glutamate (1-2 mg/gm. body weight) capable of producing blood glutamate levels many times greater than those of brain or retina has little effect on the cerebral content in rats or mice. The chemical and pathological reactions of the retina in animals so treated have not been reported.

Possible Modes of Toxic Action.—Three possibilities arise:

1. Indirect Effect: That this substance acts indirectly via adrenal stimulation (cf., Weil-Malherbe, 1949) seems unlikely, since epinephrine and substances that excite its secretion, such as glycine and *p*-aminobenzoic acid, were not injurious to the mouse retina. Large doses of the immediate metabolites of glutamate were equally ineffective, apart from aspartate, which is readily converted into glutamate by transamination in the isolated tissue (Terner, Eggleston, and Krebs, 1950). Such findings, though not conclusive, suggest that the lesion arises from the properties of glutamate itself.

2. Interference with Ionic Exchange: The in vitro studies of Terner et al. (1950) indicate that L-glutamic acid is unique among amino acids in its ability to maintain the high retinal concentration of potassium. Both ions are absorbed in approximately equivalent quantities, and the process is dependent on glucose breakdown. A massive dosage (6-8 mg/gm.) of sodium glutamate could be expected to cause some simultaneous increase in the retinal uptake of both these ions. Their association in excessive amounts within the tissue could then conceivably interfere with the outstanding level of potassium turnover that accompanies functional activity in retina. Each substance is known to promote acetylcholine synthesis in both brain and retinal preparations, but excessive potassium has the reverse effect and can, in some circumstances, inhibit ganglionic discharge.

3. Interference with Carbohydrate Metabolism: On addition to brain slices, sodium glutamate (0.01 M) causes a depression in anaerobic glycolysis which becomes maximal by one hour, after which further uptake of glutamate ceases (Weil-Malherbe, 1938; Stern et al., 1949). This effect is abolished by adding adenosinetriphosphate. In retina

exposed to the same condition, the glycolytic inhibition is far smaller (0%-6%) but the concentration of glutamate (0.01 M) used in these earlier studies was not great, being perhaps a 10th of that feasible in the plasma of the injected animal. Current investigations indicate that anaerobic glycolysis in the excised retinae of mice killed one hour after glutamate injection is about a third lower than that of a control group, whereas respiration with pyruvate as substrate is unaffected.

An unusual property of glutamate, which it shares with potassium salts and 2,4-dinitrophenol, is its ability to maintain a high rate of respiration in brain and retina. The accompanying breakdown of carbohydrate does not, however, serve a useful purpose by providing energy for the synthesis of high-energy-phosphate-bond compounds necessary for functional activity. Indeed, all three substances when added to brain slices actually reduce the content of such products (McIlwain, 1951; 1952). Not only glycolysis and acetylcholine formation but also other important enzymatic processes, such as potassium transport and the glutaminase and glutamotransferase reactions, are dependent upon supplies of adenosinetriphosphate. That certain inner layers show an unusual degree of lactic dehydrogenase (Lowry, 1955) and cholinesterase activity (Francis, 1953) is indicative of the special functions occurring in this region. The reactions named would almost certainly be affected by a deficiency of high-energy phosphate compounds if glutamate is as effective against their synthesis in retina as it is in brain. Against this hypothesis are the facts that parenteral dinitrophenol did not produce a glutamate-type lesion in the mouse and that administration of ATP with glutamate did not prevent its usual occurrence. Whether these substances are able to penetrate to the inner layers of retina is unknown.

Summary

Subcutaneous administration of sodium L-glutamate (4-8 mg/gm. body weight) damaged the retina of albino mice. Necrotic changes affected the ganglion cells, inner fiber layer, and some of the bipolar cells within a few hours of injection; the visual-cell layer was not affected. In very young animals, damage to the inner layers was more extensive and groups of rod cells protruded through the outer limiting membrane.

Sodium L-aspartate (1.27 mg/gm. body weight) produced a similar but less severe lesion when given subcutaneously to very young animals.

L-Glutamine, sodium α-ketoglutarate, 2,4-dinitrophenol, epinephrine, or ammonium salts in large dosage had no similar effect in adult mice. Claims that quinine and methanol damage the inner retinal layers in adult mice could not be confirmed.

Various biochemical systems known to be influenced by glutamate, e. g., glycolysis and potassium transport, are discussed in relation to the mechanism of the effect.

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BIBLIOGRAPHY

Birch-Hirschfeld, A.: Beitrag zur Kenntniss der Netzhautganglionzellen unter physiologischen und pathologischen Verhältnissen, von Graefes Arch. Ophth. 50:166-246, 1900.

Bruce, H. M., and Parkes, A. S.: Feeding and Breeding of Laboratory Animals: IX. A Complete Cubed Diet for Mice and Rats, J. Hyg. 47:202-208, 1949.

Druault, A.: Recherches sur l'amaurose quinique, Arch. opht. 22:19-32, 1902.

Elman, R.: The Intravenous Use of Protein and Protein Hydrolysates, Ann. New York Acad. Sc. 47:345-357, 1946.

Francis, C. M.: Cholinesterase in the Retina, J. Physiol. 120:435-439, 1953.

Gilger, A. P., and Potts, A. M.: Studies on the Visual Toxicity of Methanol: V. The Role of Acidosis in Experimental Methanol Poisoning, Am. J. Ophth. 39:63-86 (Feb., Pt. 2) 1955.

Goodman, L. S.; Swinyard, E. A., and Toman, J. E. P.: Effects of L (+) Glutamic Acid and Other Agents on Experimental Seizures, Arch. Neurol. & Psychiat. 56:20-29, 1946.

Harada, M.: Pharmakologische und histologische

Untersuchungen über die Amblyopie, hervorgerufen durch Farnkrautpräparate, Jap. J. M. Sc., IV, Pharmacol. 10:85-89, 1937.

Holden, W. A.: The Pathology of Experimental Quinine Amblyopia, Arch. Ophth. 27:583-592, 1898.

Hunt, R.: Über die Toxicität einiger Chinin-Derivate, Arch. internat. pharmacodyn. 12:497-505, 1904.

Karli, P.: Contribution expérimentale à l'étude de la pathogénie des rétinoses pigmentaires, Ophthalmologica 128:137-162, 1954.

Lowry, O. H., in Biochemistry of the Developing Nervous System, edited by H. Waelsch, New York, Academic Press, Inc., 1955, p. 350.

McIlwain, H.: Glutamic Acid and Glucose as Substrates for a Mammalian Brain. J. Ment. Sc. 97:674-680, 1951.

Phosphates of Brain During in Vitro Metabolism: Effects of Oxygen, Glucose, Glutamate, Glutamine, and Calcium and Potassium Salts, Biochem. J. 52:289-295, 1952.

Mayer-Gross, W., and Walker, J. W.: The Effect of L-Glutamic Acid and Other Amino-Acids in Hypoglycaemia, Biochem. J. 44:92-97, 1949.

Milliken, J. R., and Standen, J. L.: An Investigation into the Effects of Glutamic Acid on Human Intelligence, J. Neurol. Neurosurg. & Psychiat. 14:47-54, 1951.

Sapirstein, M. R.: Effect of Glutamic Acid on the Central Action of the Ammonium Ion, Proc. Soc. Exper. Biol. & Med. 52:334-335, 1943.

Schwerin, P.; Bessman, S. P., and Waelsch, H.: The Uptake of Glutamic Acid and Glutamine by Brain and Other Tissues of the Rat and Mouse, J. Biol. Chem. 184:37-44, 1950.

Stern, J. R.; Eggleston, L. V.; Hems, R., and Krebs, H. A.: Accumulation of Glutamic Acid in Isolated Brain Tissue, Biochem. J. 44: 410-418, 1949.

Terner, C.; Eggleston, L. V., and Krebs, H. A.: The Role of Glutamic Acid in the Transport of Potassium in Brain and Retina, Biochem. J. 47:139-149, 1950.

Weese, H.: Vergleichende Untersuchungenen über die Wirksamkeit und Giftigkeit der Dämpfe niederer aliphatischer Alkohole, Arch. Exper. Path. u. Pharmakol. 135:118-130, 1928.

Weil-Malherbe, H.: Observations on Tissue Glycolysis, Biochem. J. 32:2257-2275, 1938.

The Action of Glutamic Acid in Hypoglycaemic Coma, J. Ment. Sc. 95:930-944, 1949.

Zimmerman, F. T.; Burgemeister, B. B., and Putnam, T. J.: Effect of Glutamic Acid on the Intelligence of Patients with Mongolism, Arch. Neurol. & Psychiat. 61:275-287, 1949.

Early Components of Corneal Wound Closure

Experimental Study

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Considerable confusion exists in the literature with regard to the events leading to the closure of a penetrating corneal wound, including both early and late changes. Among early components of wound healing are included those factors operative within the first hour after the penetrating wound. These include: (1) mechanical alterations in the cornea as a result of physical stress, (2) the role of fibrin, and (3) edema. Eliminated from consideration of early changes are appreciable effects of such components as epithelial proliferation, endothelial proliferation and regeneration of Descemet's membrane, and fibroblastic repair. Although there is a sizable body of literature on this subject of corneal wound healing, there is little effort to concentrate on what occurs in a corneal wound during the period immediately after the injury.

As regards the mechanical factor, there seems to be considerable disagreement as to what actually occurs. Parsons [1] stated, "the wound is rapidly closed by apposition of the edges." Duke-Elder [2] said that, "the edges of the wound tend to remain opposed in the deeper parts and only the superficial portions tend to gape. Immediately the wound is made, imbibition of fluid makes the edges swell and turn opaque, thus together with the outpouring of exudate material tends to bring the wound edges in apposition. When the edges of the wound are in apposition, coaptation first occurs in the central area while anteriorly and posteriorly the peripheral part is retracted by the elasticity of the tissue and tends to gape, leaving an anterior and posterior triangle where the lips of the wound pout apart." Weinstein [3] seemed to appreciate the retraction of Descemet's membrane and the posterior corneal lamellae in the rabbit. Samuels [4] discussed the very important role of Descemet's membrane and its tendency to retract after penetrating incisions. Dunnington [5] mentioned that "in the initial stages the normal retractivity of the tissues produces separation of the anterior and posterior edges of the wound."

The role of fibrin in closure of corneal wounds in the rabbit has been appreciated by Weinstein,[3] Brown and Nantz,[6] Tassman,[7] and, more recently, by Binder and Binder.[8] Parsons [1] and Gradle [9] seemed to consider the role of fibrin as important in corneal healing of the human. However, opinion has been given by many authors that fibrin has no role in human healing,[7] a very questionable role,[6] or even a detrimental effect on the healing process.[10] The basis of the first two opinions that fibrin is unimportant seems to be that the primary aqueous in the human contains traces [11] or no [6] fibrinogen. However, in a gaping draining corneal wound, we are not concerned with the protein content of the primary but with that of the secondary aqueous. The protein increase of human secondary aqueous is generally reported as small compared with animals.[12,13] The ability of human secondary aqueous to clot is also disagreed upon, although there is general agreement on the coagulability of rabbit aqueous.[14]

The chronology of stromal edema which occurs after penetrating wounds is not well

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assessed in the literature. Cogan [15] mentioned that edema increases and reaches its maximum within the first two hours, but these observations are concerned only with endothelial wounds. Duke-Elder [2] stated that "immediately the wound is made, imbibition of fluid by the corneal lamellae makes the edges swell and turn opaque. Together with the outpouring of exudative material, this tends to bring the edges into apposition. If the wound is oblique and valvular, coaptation is rapid, and in favorable circumstances cohesion may be sufficient to withstand the intraocular pressure within one-half hour." Dunnington [5] stated, "My experiments as well as those of Ashton and Cook have confirmed the earlier observations that primary closure of any corneal incision is affected through swelling of the corneal lamellae produced in large part by imbibition of aqueous humor."

In view of the uncertainty of the importance and sequence of the early components of corneal wound healing, experiments were designed to observe the course of healing of corneal incisions, with and without the presence of fibrin, in several species of animals including man.

Healing of Corneal Incision in Rabbits

A central horizontal corneal incision 5 mm. long and penetrating into the anterior chamber was made on a series of rabbit eyes. These eyes had been previously treated with 1 drop of topical tetracaine (Pontocaine) hydrochloride for anesthesia. The events occurring in each eye during the course of the first hour were continuously observed with the high-power ocular in a Universal slit lamp. Photographs were made and representative eyes were removed for histologic section at intervals during this hour.

Immediately after the incision was made, the anterior chamber collapsed, the collapse being complete except at the immediate junction of the pupillary margin with the lens, where a fine separation of the lens and the cornea could be made out with the fine beam and the high-power ocular. The edges of the wound took on a gray-white color which could be seen by direct examination with the hand light as well as with the slit lamp. The edges of the wound under the slit lamp showed a laminated appearance similar to that seen in lamellar separation in an intumescent cataract. This lamellar appearance assumed the form of striations parallel to the incision and was seen along the entire cut surface. Thus, the normally invisible stromal lamellae became immediately visible. As seen from the front, the wound edges gaped in a characteristic elliptical fashion, the widest separation located midway between the ends of the wound. The portion of the corneal stroma that most closely approximated its mate on the other side was approximately at the junction of the anterior one-third with the posterior two-thirds. There was wide posterior gaping of the wound in all cases, so that the posterior edge of the

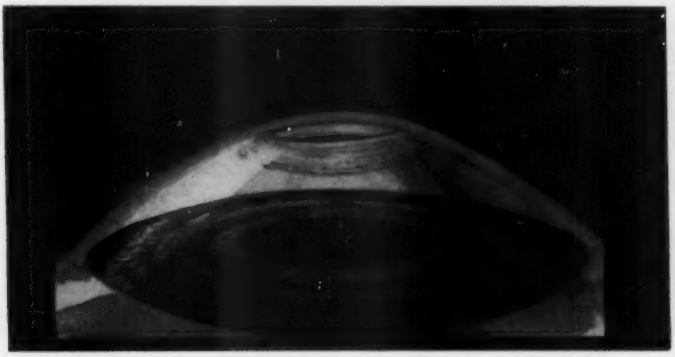


Fig. 1.—Drawing of an eye one-half hour after a central corneal incision, in which the characteristics of wound retraction and the striated appearance of the wound edges are shown. The fibrin cast is not illustrated.

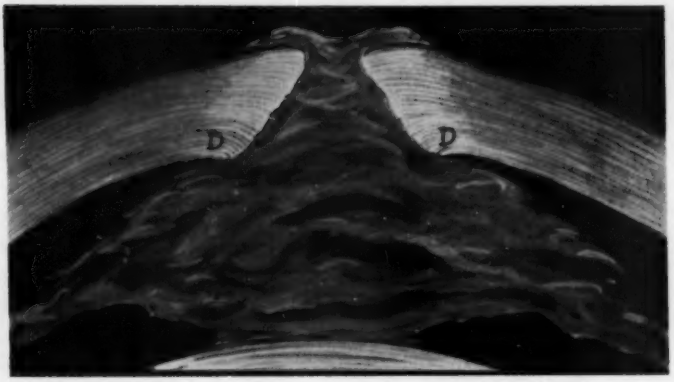


Fig. 2.—Composite drawing of the slit lamp appearance of an eye one-half hour after corneal incision. The fibrin plug (*F*) is continuous from the anterior chamber through the wound onto the anterior surface of the cornea. The aqueous anterior to the fibrin cast contains a heavy beam (*B*). The retracted edge of Descemet's is shown at *D*.

wound retracted four to five times the amount of the closest approximation of the wound edges, perhaps because of the elasticity of Descemet's membrane or of the posterior aspect of the stroma. There was a mild retraction tendency of the very anterior aspect of the wound, with a slight bulging tendency at the point part way down in the stroma, as described (Figs. 1 and 2).

The anterior-posterior thickness of the wound immediately became one and one-half to two times the thickness of the normal cornea. Because fanning-out of the cut edge of the corneal stroma was so rapid, it was thought to be a release of normal physical stresses rather than a result of edema. This lengthening of the anterior-posterior corneal thickness at the wound edge was compensated for by one of two mechanisms. In some cases there was a slight anterior puckering of the wound with an increase in curvature of the cornea at the wound edge. In others there was a protrusion of the cornea posteriorly into the anterior chamber, abutting against the lens. The entire cut edge of the wound from epithelium to endothelium lengthened considerably (Fig. 2). There was no approximation of the edges except occasionally at the extreme 10% of the wound length. With use of a wider beam of the slit lamp, the curvature of the cut edge of Descemet's membrane appeared altered, looking very much like a wrinkle parallel to the edge of the incision.

It should be stressed that all of the above features were noted as soon as the eye could be brought into focus under the slit lamp after the incision. This time varied from 30 seconds to 2 or 3 minutes. Various phases of the phenomenon were concentrated on in different animals so that the chronology could be established. Thus most of these changes were considered to be results of the mechanical alteration of the physical stresses within the cornea rather than the development of a secondary process such as edema.

Usually beginning within two or three minutes, a generous amount of straw-colored fibrin appeared between the wound edges. The amount increased rapidly during the next few minutes, until numerous strands of fibrin extended from one edge of the wound to the other (Fig. 3A). Within periods varying from 3 minutes to 1 hour, with an average of about 10 minutes, this fibrin completely sealed the gap between the wound edges. As soon as the wound was plugged with fibrin, the anterior chamber formed. When the anterior chamber was formed, a dense cast of clotted fibrin became visible (Fig. 2). This extended back from the wound in pyramidal fashion to cover the pupil and part of the iris. Other less dense fibrinous material filled the remainder of the anterior chamber. In addition, fibrin emanated from the wound gape and rapidly coagulated in the conjunctival sac (Fig. 4A). Within 30 minutes, this

Fig. 3A.—Photograph through slit lamp (high-power, four-minute exposure) of incision made in living nonheparinized rabbit eye one hour previously. Fibrin plug (*F*) is seen between wound edges and extending into anterior chamber, which is deep. Arrows indicate wound edges.

Fig. 3B.—Similar photograph in living heparinized rabbit. Note wound gape with no fibrin between edges; anterior chamber is seen to be flat.

Fig. 3C.—Similar photograph of rabbit which was dead at time of incision. Complete absence of fibrin is noted. Differential wound retraction and flattened chamber are well illustrated.

coagulated mass of gelatinous material filled the inferior fornix, with fibrin strands continuous with the fibrin plug in the wound and anterior chamber. When in some cases the wound became plugged unusually rapidly by fibrin, there was a deficiency of fibrin in the conjunctival sac, while in those cases which continued to leak (for example) more than one-half hour the entire conjunctival sac became filled with clotted fibrin. This seemed to indicate that the source of the fibrin in the conjunctival sac was from the anterior chamber. As the hour progressed, even after initial sealing of the wound, the plug became denser in appearance and more opaque and there were more and thicker bands bridging the wound.

It should be emphasized that there was a direct relationship between the completion of the fibrin "corking" of the wound and the formation of the anterior chamber. In some cases where the anterior chamber took longer to form, the fibrin plug appeared incomplete. Even after the wound was completely plugged and the anterior chamber had re-formed, the wound edges were still not approximated. In other words, the fibrin acted as a cork and not as physiologic glue causing adherence of the wound edges. In some cases after the chamber had been re-formed, struggling of the animal caused the chamber to collapse, and the fibrin plug became visibly dislodged. With the re-formation of the plug, there was noted a concomitant re-formation of the anterior chamber. In two eyes corked with a fibrin plug, gentle removal of this plug with forceps caused the anterior chamber casts to come forward in the wound, which was immediately replugged, with resultant re-formation of the anterior chamber. Removal of this secondary plug caused an immediate collapse of the chamber until the plug re-formed.

The changes which took place in the wound edges during the course of the hour's observation were few. No tendency for approximation of the wound edges could be seen, although examination at this time was difficult because of the presence of the opaque fibrin plug. The characteristics of the gape after removal the plug by forceps were unchanged over the initial observation. During the course of the hour, the adjacent stroma became slowly and progressively more gray, suggestive of edema.

In summary, these observations on the healing of a corneal incision in rabbits showed (1) immediate retraction of the wound edges, especially posteriorly; (2) formation of a fibrin plug in the wound; (3) re-formation of the anterior chamber simultaneously with completion of the fibrin "cork"; (4) little tendency within the first hour toward approximation of the wound edges by swelling or any other means, although the adjacent corneal stroma slowly developed some haziness suggestive of edema.

Effect of Heparin on Healing of Corneal Incisions in Rabbits

In this series, the rabbits received 10,000 units of sodium heparin intravenously at least 15 minutes prior to the central corneal incision. In these eyes of heparinized rabbits, all the clinical and histological characteristics of corneal wound healing described previously for the normal rabbits were present except that fibrin formation was absent (Figs. 3B and 4B). The lack of fibrin left a continuous through-and-through opening between the anterior chamber and the outside. As a consequence, the anterior chamber remained flat during the entire period of observation, except for some cases in which there was a slight amount of space visible under high power between the lens and pupillary border. In some cases where the bulging posterior edge of the wound abutted against the lens, there was a microscopic formation of the anterior chamber corresponding to the amount of posterior abutment. Aqueous passed through the gaping wound in a continuous flow during the

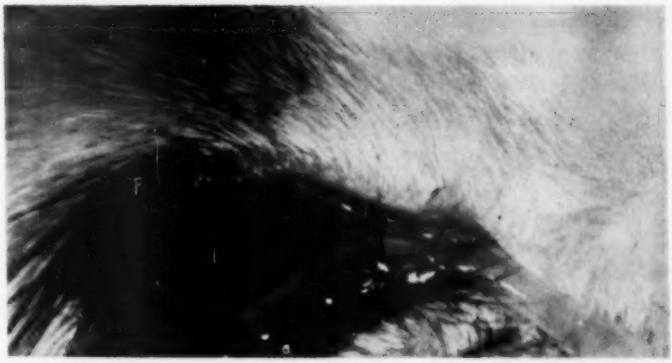


Fig. 4A.—Nonheparinized rabbit one-half hour after operation. Clotted fibrin is seen in conjunctival sac and over lower lid.

period of observation on these heparinized animals. A few flecks of fibrin occasionally appeared at the lower edges of the wound, and, because of their loose attachment, they were at times washed away by the force of the aqueous stream. The wound edges were not approximated by edema.

Corneal Wound Healing After Death

In additional rabbits a central corneal incision was made immediately after the animal had been killed by injection of air intravenously. There was a complete lack of fibrin which was even more pronounced than in the heparinized animals (Fig. 3C). The other characteristics of wound healing were similar to those in the previous two experiments. A narrow anterior chamber tended to persist in front of the lens, as if the collapse of the choroidal circulation had produced a lack of positive posterior pressure to cause complete collapse of the anterior chamber. No continuous aqueous flow was seen from these wounds.

Healing of a Posterior Corneal Incision

In other normal and heparinized rabbits a posterior incision about one-third through the cornea was made by a discission knife introduced through the limbus. In the normal rabbit the edges of the wound retracted widely in an elliptical manner and the wound edges assumed a lamellar appearance. Within one minute fibrin filled the anterior chamber. This fibrin cast originated in the wound and triangulated posteriorly, being similar to the casts seen after the penetrating incision. In the heparinized rabbit the characteristics of the posterior corneal wound were similar except for the lack of fibrin. The aqueous ray became positive.

Healing of an Anterior Corneal Incision

In contrast to the posterior corneal incision, an incision into the anterior one-half of the cornea of a nonheparinized rabbit produced relatively little retraction of the edges, no fibrin response in the anterior chamber, and little or no fibrin in the con-

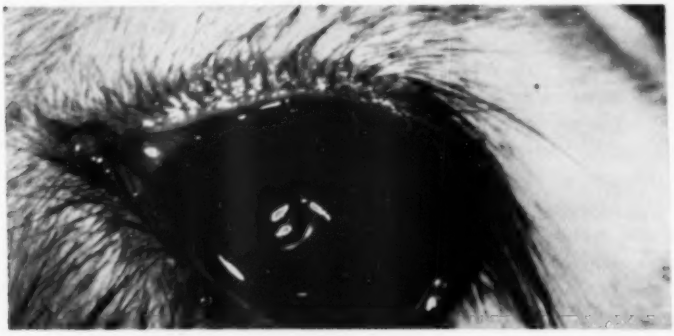


Fig. 4B.—Heparinized rabbit one-half hour after operation. No fibrin clot is seen.

junctival sac. This again indicated that the source of the fibrin was the secondary aqueous.

Healing of Corneal Incisions in Other Species

In cat, dog, and monkey eyes no difference was noted between the course of corneal healing in either normal or heparinized animals, compared with the normal and heparinized rabbits. All showed differential wound retraction, striated appearance of wound edge, increased edema of stroma, and gradual building up of the fibrin plug, the completion of which coincided with re-formation of the anterior chamber. In the heparinized cats an interesting phenomenon was noted. A beam of moderate intensity appeared in the aqueous after incision. The same continuous aqueous flow was seen through the wound. In addition, many fine particles (red blood cells) moved rapidly with the stream, dramatizing the rapid flow of aqueous through the wound and onto the cornea. The wounds of these heparinized animals were still filtering after one hour of observation. It was felt that the appearance of red blood cells was merely a further step in increased capillary permeability caused by the decompression, the first step being a mild beam; the next, a fibrin response, and the last, red blood cells.

Corneal Wound Healing in Humans

Four patients were studied in a similar manner under the slit lamp. After tetracaine anesthesia, a 4 mm. incision was made in the center of the cornea of the first eye, about to be enucleated for absolute glaucoma. The geometric characteristics of the wound were essentially the same as in the animal experiments except that the degree of posterior gaping was relatively less than in the animal eyes, and the over-all wound gaping was less. After five minutes, fibrin began forming between the wound edges and in a downstream fashion over the wound edge inferiorly. The anterior chamber formed after the wound became plugged by fibrin within 10 minutes. The fibrin gradually built up over the next half hour and firmly plugged the wound. By the time the eye was enucleated, three hours later, the plug was so strong that even the extensive manipulation of the enucleation was done without rupture of the wound or loss of anterior chamber.

A second eye about to be enucleated was similarly studied. The incision was small (2.5 mm.) and the chamber re-formed almost immediately, perhaps by edge-to-edge apposition of the wound plus fibrin. In this case there was no extensive drainage of the wound, and so the fibrin response was minimal, suggesting that the source of fibrin was the secondary aqueous. Histological study of this eye showed a protein exudate in the anterior chamber, probably fibrin.

A third eye, discussed by Dr. William F. Hughes, was studied after corneal transplantation. The eye was noted to have a negligible aqueous beam before removal of sutures. The patient moved during the procedure and ruptured the wound in one area. Observations under the slit lamp showed that the aqueous became filled with fibrin, and the wound sealed itself with rapid reformation of the anterior chamber.

The eye of a fourth human patient was incised before enucleation and studied similarly. The edges of the wound remained separated, and fibrin gradually appeared between them. When observations had to be discontinued in one-half hour, the fibrin plug was not quite complete, and therefore the chamber remained flat. Also, several independent collections of red blood cells appeared over the iris, well away from the point of surgery. It was believed that, as in the cat, dog, and monkey eyes, this phenomenon represented just an exaggeration of the normal increased capillary permeability resulting from decompression. In the human eyes the gaping was not as great as in the eyes of the other species. With a fine beam of the slit lamp under high power, however, lack of edge-to-edge apposition could be seen.

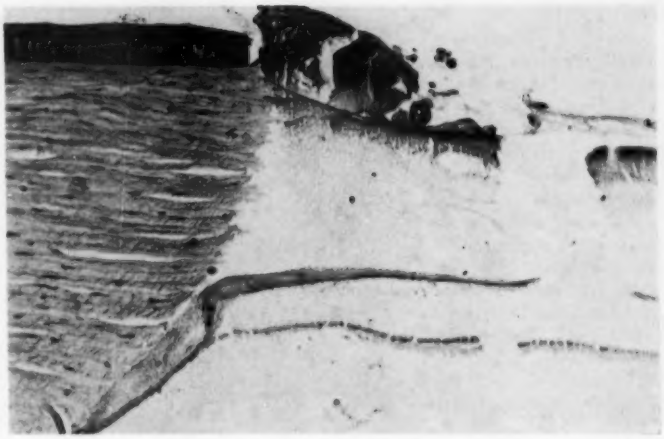


Fig. 5.—Central corneal incision in nonheparinized rabbit 12 minutes after surgery (high-power magnification). One edge of the wound is seen, and fibrin is noted to be bridging the wound. The thickening of the stroma as seen under the slit lamp is not so evident in the fixed specimen. The dehiscences in the plug are artefacts.

Histological Findings

The histological findings in these experiments corroborated the slit lamp findings. In Figure 5, twelve minutes after a central corneal incision in a nonheparinized rabbit, the fibrin plug is well formed. (The dehiscences in the fibrin plug are artefacts caused by sectioning.) The fibrin plug attaches to the fractured ends of the lamellae and passes directly to the opposite side. The anterior chamber had re-formed in this eye at the time of sectioning, in spite of a wide stromal gaping. Posterior retraction of the cut lamellae is seen as well as fanning out of the lamellar cells. Stromal edema adjacent to the wound edge does not show up very well on these fixed specimens. Retraction and curling of the end of Descemet's membrane is present. After one hour the fibrin plug is more densely formed (Fig. 6), completely sealing the fractured ends of the lamellae and insinuating itself between the gaping ends of the wound. The posterior lamellae retract most, and the closest approximation of the edges is near the junction of the anterior one-fourth and posterior three-fourths. In the one-hour sections there seems to be a deficiency of the corneal corpuscles at the region of the wound edge.

The histological findings in the heparinized rabbit is similar except for the relative absence of the fibrin response (Fig. 7).

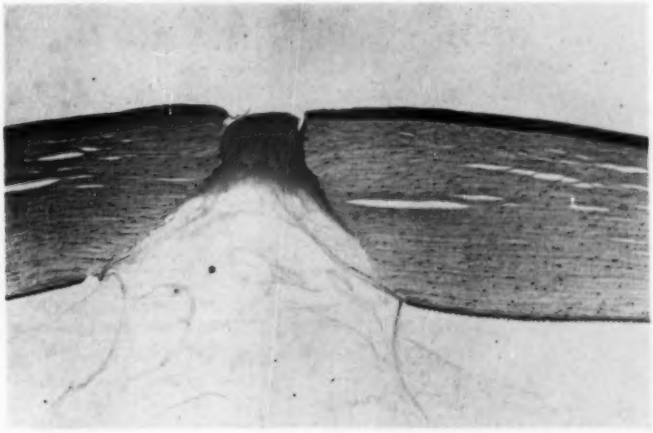


Fig. 6.—Nonheparinized rabbit one hour postoperatively. The wound is well sealed by the fibrin plug, which originates in the anterior chamber and is attached firmly to the cut edges of the lamellae from epithelium to endothelium. Greater retraction is present posteriorly than anteriorly. Stromal corpuscles are scarce near the wound.

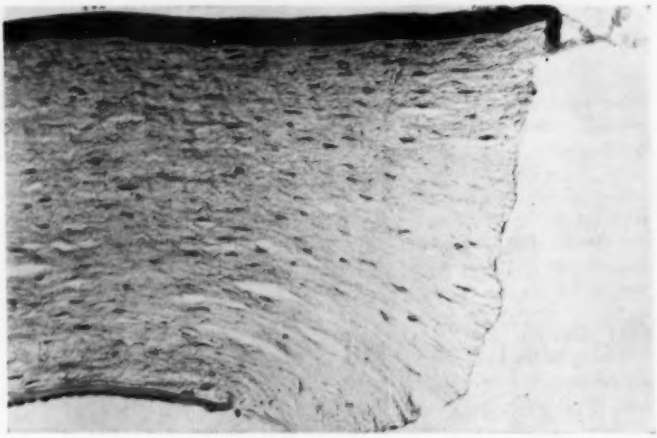


Fig. 7.—Heparinized rabbit one hour postoperatively. High-power photograph shows the absence of fibrin, the beginning participation of the epithelium in the healing process, generous fanning out of the lamellae with posterior direction of the posterior lamellae, and retraction and curling of Descemet's membrane. This shows, as in Figure 6, a sparsity of stromal cells near the region of the wound.

The histological findings in dead rabbits confirm the slit lamp findings, except that the edema seen clinically after one hour was not visible histologically. The section was similar to that of the living heparanized animal eye except that there was no trace of fibrin in the slide (Figs. 8A and 8B).

A posterior incision in a nonheparinized rabbit is illustrated in Figure 9A, one hour after incision. As with the penetrating incision, there is a marked fibrin response. The fibrin seems to attach firmly to the severed ends of the retracted lamellae. When the same thing is done in a heparinized animal (Fig. 9B), fibrin is strikingly absent. In this case the posterior incision went approximately half way through the cornea, and a marked retraction of the lamellae and Descemet's membrane are seen. There is apparently a deficiency in the lamellar cells in the region of this posterior incision also.

An anterior nonpenetrating incision one hour postoperatively in a living nonheparinized animal shows almost no fibrin response, a minimal tendency toward retraction of the anterior lamellae, and a relative paucity of stromal cells in the immediate area of of the wound (Fig. 9C). This illustrates that healing of anterior incisions is carried on during the early stages by the epithelium. In the dead animal (Fig. 9D), approximately the same thing occurs, except that in this eye the healing process of the epithelium seems retarded.

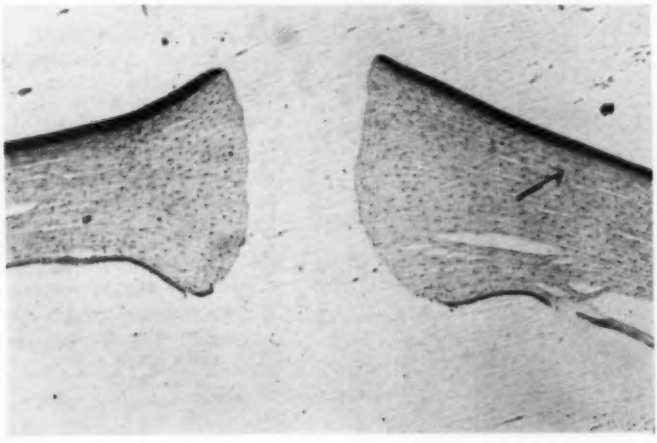


Fig. 8.—Twelve minutes after central corneal incision in a rabbit which had been dead three minutes. There is a complete absence of the fibrin response, characteristic fanning of the wound edges, and a tendency for anterior as well as posterior protrusion of the thickened lamellae.

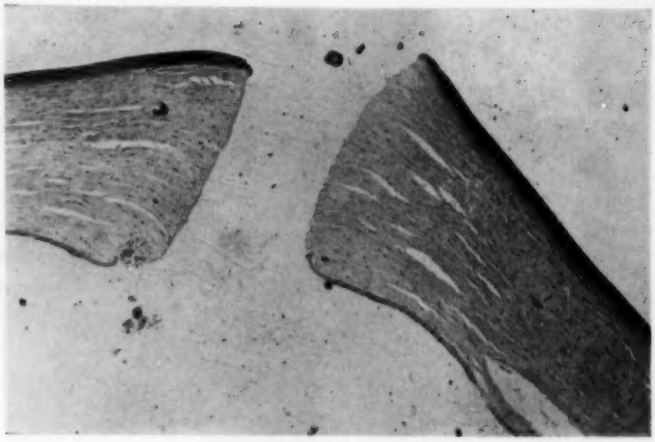


Fig. 8B.—One hour after central corneal incision in a rabbit which had been dead 15 minutes. Total fibrin paralysis is evident, as are the other characteristics of the heparinized animal. Paucity of stromal cells in region of wound. In addition, beginning participation of the epithelium in the healing process is seen even in the dead animal.

Fig. 9A.—Posterior corneal incision in living nonheparinized rabbit one hour after surgery. A generous anterior chamber fibrin response is seen, with the densest accumulation and attachment of the fibrin at the cut edges of the stromal lamellae. Retraction of the lamellae is seen. This also was a typical response.

Fig. 9B.—Living heparinized rabbit with posterior corneal incision, one hour after operation. The fibrin response is blocked by heparin. This shows a marked tendency for the posterior stroma and Descemet's membrane to retract instead of being approximated. There is a very gentle curve because of this retraction tendency. There is a complete fibrin paralysis; edema of the posterior stromal cells can be seen, and there is a mild forward bowing of the cornea.

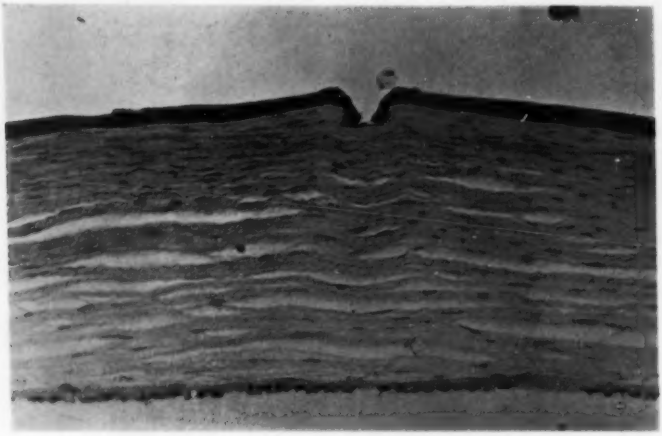
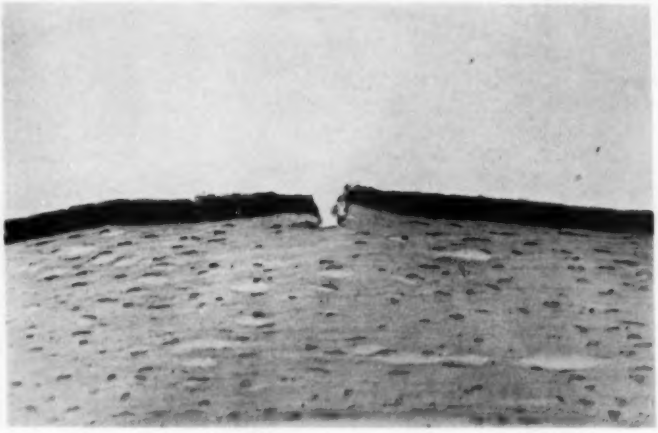


Fig. 9C.—Living nonheparinized rabbit with anterior incision, one hour after operation. There is no fibrin response. There is a deficiency of the stromal cells adjacent to the wound. Beginning participation of the epithelium in the closure of this wound is noted. Retraction tendency is minimal in anterior incisions.

Fig. 9D.—Dead rabbit with a central anterior lamellar incision made one hour previously. Little tendency toward retraction is noted. A deficiency of the stromal cells in the region of the incision is seen.



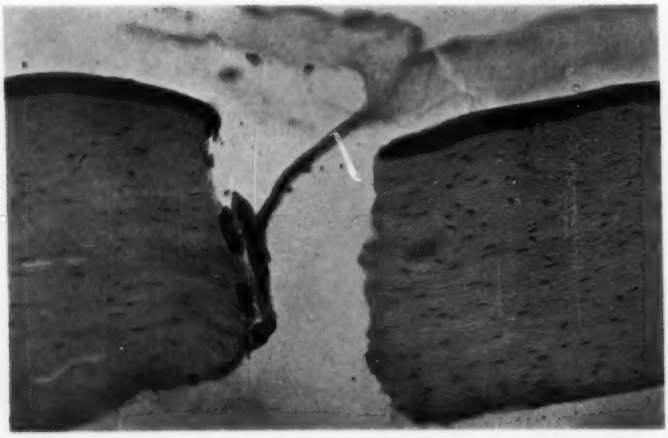
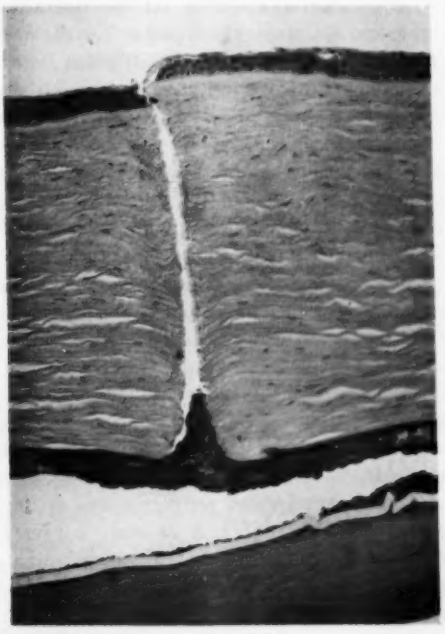


Fig. 10A.—Living nonheparinized monkey eye one hour after operation. A greater posterior than anterior retraction is seen. The fibrin plug is seen to have been sealing the wound edges. The separation of the wound edges occurred during processing.

Histologic findings in the cat, dog, and monkey were essentially the same as in the rabbit. One hour after central corneal incision into a nonheparinized living monkey, the cornea shows posterior retraction of the wound edges, lack of edge-to-edge apposition of the wound, a generous fibrin plug which had been sealing the wound, and stromal thickening (Fig. 10A); all are similar to findings in the rabbit. In the heparinized monkey the findings are similar to those in the heparinized rabbit, in which the fibrin plug is deficient (Fig. 10B). There is less tendency for the wound edges to gape in this eye.

Histological findings in human eyes did not differ essentially from the observations in other species (Fig. 11). There is less of a gaping tendency in these eyes as compared with the animal eyes. The fibrin plug does not seem quite as dense as in animal eyes. The fibrin plug can be seen between the edges of the wound.

Fig. 10B.—Living heparinized monkey eye one hour postoperatively. Lack of fibrin and lack of stromal apposition is seen. Iris prolapse is present, and the anterior chamber is flat. There is little differential retraction in this picture.



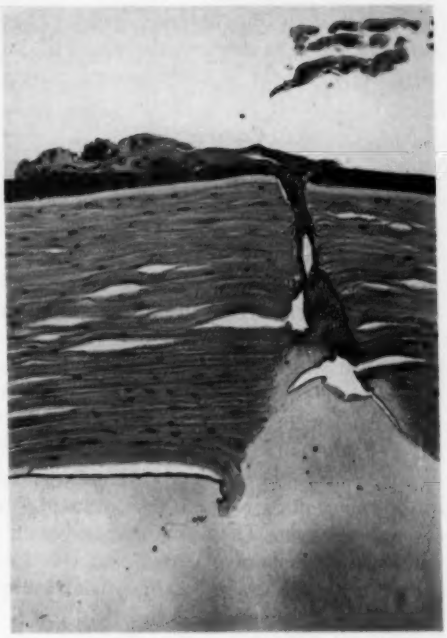


Fig. 11.—Human eye two hours after incision. A good fibrin plug is seen sealing the wound.

Review of 13 human eyes which had incurred penetrating or lacerating injuries showed that none had edge-to-edge apposition of the stroma. Fibroblasts were always present between the stromal edges. Since these fibroblasts normally grow into a fibrin matrix and require such a matrix as a prerequisite to their appearance, these findings were corroborative evidence that such a matrix existed in the earlier stages of the healing process.

A review of 46 rabbit eyes which had been the subject of a previous study [16] on corneal wound healing showed that there was no edge-to-edge apposition of the stroma. The lamellar fibers were always separated by either a fibrin plug or a fibroblastic plug. Eyes enucleated less than three days from the time of surgery showed a fibrin plug, while those enucleated later had a fibroblastic one. In addition, these eyes had an anterior triangle of epithelial cells between the wound edges. There was also a greater posterior gape in these sections as

compared with the anterior gape. These findings seem to confirm the essential importance of fibrin in early wound closure.

Comment

Of the three early factors in corneal wound closure in the rabbit eye, the mechanical factors, the fibrin phase, and the edema, the most important of these is the fibrin phase. Fibrin is the *sine qua non* of early wound closure. This fibrin originates from the secondary aqueous, as shown by its absence in anterior corneal incisions and its presence in posterior corneal incisions. It is so fundamental, as Binder and Binder [8] have shown (their results were confirmed in our laboratory), that early wound closure in the rabbit does not even take place in the absence of fibrin. They produced and maintained flat chambers in the rabbit eye for periods of days simply by maintaining heparinization of animals which had a similar central corneal incision. They implied that without fibrin the epithelium has no roadbed to travel over in bridging the wound and may grow down into the anterior chamber or on the underside of the cornea. Fibrin, by providing a skeleton through which fibroblasts travel after a few days, also seems to expedite the later fibroblastic phase of wound healing. All of these experiments were performed on rabbits, which have a secondary aqueous containing a great deal of fibrin.

There has been a tendency on the part of workers on the problem to discount the fundamental role of fibrin in corneal wound healing in humans. The basis for this assumption is that human secondary aqueous has been reported to have much less fibrinogen than that of the rabbit. Let us examine the evidence to the contrary. Systemic wound healing in the human has an important fibrin phase, which is universally recognized by students of the problem.[17] Ocular healing in the various species studied is similar to that of the human in all other phases of wound healing, such as the epithelial phase, the fibroblastic phase, the endothelial phase, and the edema phase. The assumption that human corneal wound healing has a fibrin phase is logical, unless evidence to the contrary is presented. Yet, no such evidence is forthcoming. It is difficult to accept the idea that human corneal wound healing is unique, differing fundamentally from wound healing elsewhere in the human body and also differing fundamentally from the type of corneal wound healing studied here in the rabbit, cat, dog, and monkey eye. Fibrin is certainly available in the human eye. Certain types of iritis in human beings are associated with a fibrin cast in the anterior chamber. In postoperative healing under a conjunctival flap there is a ready supply of fibrinogen from the conjunctival vessels independent of any secondary aqueous. The human experiments described previously in corneal wound healing confirm the thesis that fibrin becomes available in the secondary aqueous of humans and corks the wound soon after an incision has been made.

Several practical applications of this concept immediately come to mind. The formation of a fibrin plug encourages re-formation of the anterior chamber on the operating table and maintains the chamber for the first several days after surgery, until other, later, components of wound healing make their appearance. Our study suggests that certain common complications of intraocular surgery occurring soon after penetrating incisions, such as persistent flat chamber, early wound fistulization, and prolapse of intraocular contents, may be etiologically related to fundamental defects in the fibrin mechanism. The evidence for these suggestions is that fibrin paralysis by heparin in these experiments caused a persistent flat chamber, a continuously fistulizing wound, and a structurally deficient wound which would invite prolapse of the intraocular contents.

The maintenance of active aqueous fistulization in fibrin-deficient animals suggests that inhibition of fibrin formation might promote fistulization after glaucoma surgery, as suggested by Bick and Haines.[18]

Histologically it appears that the fibrin plug blocks the downgrowth of conjunctival and corneal epithelium into the anterior chamber, a most dreaded complication after cataract extraction. It is not inconceivable that this unfortunate sequel might be partly caused by a deficient fibrin plug. Perhaps indiscriminate irrigation of the anterior chamber during cataract surgery may be undesirable because it substitutes saline for secondary aqueous, rich in fibrin. The large posterior retraction of Descemet's membrane and corneal stroma following an incision creates a posterior gape which is first filled with a fibrin plug and later by fibroblasts. A certain amount of this posterior gaping must be regarded as part of the expected result of incision and not solely as an indication of malplaced sutures.

Edema of the corneal stroma, which develops gradually during the first hour, does not seem to be an important factor in wound apposition during the early period of the first hour, as suggested by Duke-Elder, Dunnington, and others.

Conclusions

Because of the uncertainty of the importance and sequence of events in corneal wound healing during the first hour after incision, experiments are reported concerning the clinical and histological course of healing of corneal incisions in rabbits, cats, dogs, monkeys, and humans. The important stages during this early period include the following:

1. An immediate retraction of Descemet's membrane and posterior layers of the cut stroma, which produces a large inverted-V-shaped gaping of the incision posteriorly. To a much less extent, gaping of the anterior layers occurs. These immediate results of corneal incision are probably due to a release of physical tensions and elastic tissue in the cornea.

2. Rapid formation of a fibrin plug, as early as 3 to 10 minutes after incision through the posterior layers, which seals the wound and permits re-formation of the anterior chamber. This fibrin is largely derived from secondary aqueous. Inhibition of the formation of this fibrin plug can be accomplished by systemic heparinization of the animals.

Edema of the corneal stroma develops very slowly during the first hour and seems of little importance in producing coaptation of the edges of the wound during this period.

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REFERENCES

1. Parsons, J. H.: The Pathology of the Eye, London, Hodder & Stoughton, Ltd., 1904, Vol. 1, pp. 151-156.

2. Duke-Elder, S.: Text Book of Ophthalmology, Vol. 4, St. Louis, The C. V. Mosby Company, 1949, pp. 5975, 6004-6005.

3. Weinstein, A.: Experimentelle Untersuchungen über den Heilungsprocess bei perforirenden Schnittwuden der Hornhaut, Arch. Augenh. 48: 1-50, 1903.

4. Samuels, B.: Internal Gaping of Corneal Wounds After Injuries and Operations, Tr. Ophth. Soc. U. Kingdom 72:327-342, 1952.

5. Dunnington, J. H.: Ocular Wound Healing with Particular Reference to Cataract Incision, A. M. A. Arch. Ophth. 56:639-659, 1956.

6. Brown, A. L., and Nantz, F. A.: Corneal Healing: Adhesive Power of Aqueous Fibrin in the Rabbit, Am. J. Ophth. 27:1220-1224, 1944.

7. Tassman, I. S.: Experimental Studies with Physiological Glue (Autogenous Plasma plus Thrombin) for Use in the Eye, Am. J. Ophth. 33:870-878, 1950.

8. Binder, R., and Binder, H.: Experimentelle Untersuchungen über den Einfluss von Anticoagulantien auf die Heilung von Hornhautschnittwunden, von Graefes Arch. Ophth. 155:337-344, 1954.

9. Gradle, H. S.: The Present Status of Keratoplasty, Am. J. Ophth. 4:895-899, 1921.

10. Dunnington, J. H., and Regan, E. F.: The Effect of Sutures and of Thrombin upon Ocular Wound Healing: Jackson Memorial Lecture, Am. J. Ophth. 35:167-177, 1952.

11. Duke-Elder, S.: Text Book of Ophthalmology, Vol. 1, St. Louis, The C. V. Mosby Company, 1932, p. 429.

12. Duke-Elder, S.: Text Book of Ophthalmology, Vol. 1, St. Louis, The C. V. Mosby Company, 1932, p. 441.

13. Deleted.

14. Bellows, J. G., and Chinn, H.: Regeneration of the Aqueous, Arch. Ophth. 24:1144-1166, 1940.

15. Cogan, D. G.: A New Method for Studying Endothelial Regeneration: Biomicroscopic Observations on Normal and Vitamin C Deficient Animals, Ophthalmologica 118:440-443, 1949.

16. McDonald, J. E., and Wilder, H. C.: The Effect of Beta Radiation on Corneal Healing, Am. J. Ophth. 40:170-180 (Nov., Pt. 2) 1955.

17. Arey, L. B.: Wound Healing, Physiol. Rev. 16:3327-3406, 1936.

18. Bick, M. S., and Haines, R. W.: Local Use of Heparin in the Eye: Pellet Implantation at an Experimental Filtering Site, Am. J. Ophth. 32: 774-780, 1949.

The Illusion of a Primary Melanoma of the Optic Disc

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Tumors of the optic disc are extremely rare. Up to the present only about 30 cases have been published, a few with microscopic study. If we subtract from this number those which originate from the surrounding tissue, i. e., malignant melanomas of the choroid, retinoblastomas of the retina, and metastatic tumors, which are likewise very rare, then the remaining number of tumors of the optic disc is considerably smaller. Among the latter pigmented tumors, neural tumors and tumors in phacomatosis have been described.

In the present paper we are chiefly interested in pigmented tumors of the optic disc. Up to the present only 10 of these have been described, and each one was reported as a primary tumor of the optic disc (Murray, Vasquez-Barrière, Oloff, Cosmetatos, Speciale-Cirincione, Oguchi, Levine, Bucalossi, Fry and Delong, Cordes and Hogan).

The various authors differ considerably in their estimation and consideration of these cases as primary pigmented tumors of the optic disc. Nordmann [4] mentions only one primary pigmented tumor of the optic disc, while Oguchi [3] even considers the diagnosis of tumor of the optic disc doubtful if the choroid encroaches the least part in the pathological process. Reese [6] includes eight cases of this kind of tumor, and for one of these cases there is no histologic finding (Oloff). Cordes and Hogan [10] have five cases; Duke-Elder,[5] six (including that of Speciale-Cirincione, while on page 3095 the latter is represented as a primary tumor of the optic disc and on page 2486 the same case is considered as a juxtapapillary malignant melanoma of the choroid. DeVeer [8] discusses in detail all 10 cases published and cited by various authors as primary pigmented tumors of the optic disc and draws the conclusion that in none of these cases has it been possible to exclude with certainty the encroachment of the choroid in the pathological process or else to prove the primary origin of the pigmented tumor in the optic disc itself. According to deVeer,[8] in the case of Levine it is by no means out of the question that it is a case of metastatic tumor, while in the cases of Oguchi, Cordes, and Hogan he considers that they cannot be undoubtedly accepted as primary tumors of the optic disc, as the serial sections of the tumor did not include the margins of the optic disc and neighboring choroid. For this reason, deVeer is of the opinion that the possibility of a juxtapapillary malignant melanoma of the choroid can by no means be excluded and that the undoubted origin of a tumor of the disc cannot be taken for granted. Considering that for more than 50 years there has been no convincing proof of the existence of primary pigmented tumors of the optic disc, it may be that such a disease does not exist (deVeer [8]).

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From the University Eye Clinic.

Report of a Case

The case which we are going to report is interesting from two points of view—on the one hand because of the clinical picture and on the other because of the pathoanatomical correlation.

A 30-year-old woman entered the clinic on Sept. 22, 1954. In her childhood she had had eye trouble, and in 1948 had an extrauterine pregnancy. Her father died of tuberculosis; her mother, of a brain tumor. Her present illness had begun three months previously, when she began to have attacks of headache with loss of consciousness. She

was treated as an outpatient by a neurologist, but with no results. She was directed to the eye clinic for an examination of the fundus and was kept there, as a papillary tumor of the left eye was suspected.

The patient was poorly developed and nourished; her skin was very dark, but with no blemishes.

There were no changes in the eyes except for a bilateral superficial clouding of the peripheral cornea. The pupils reacted normally; the lens was transparent; the vitreous body was normal. The fundus of the right eye was also normal. In the left eye the fundus revealed a tumor one and one-half times the disc diameter, elevated about 1 D. and poorly defined. It arose from excavation of the disc and had a grayish green color and an uneven appearance. The lower blood vessels of the disc were partly covered and partly pushed aside by this growth. The vessels of the retina were normal in size. There was a linear hemorrhage on the upper and temporal margin of the optic disc. The reflexes of the macula were poorly defined (Fig. 1). Vision O. D., 0.3; O. S., 0.3-0.4. Skiascopy of the right eye showed a +2 refraction in the horizontal and −4 in the vertical meridian; skiascopy of the left eye showed +0.5 horizontally and −4 vertically. The intraocular pressure was normal in both eyes. The field of vision on the left side showed an extension of the blind spot.

Fig. 1.—Aspect of tumor on the left optic disc at beginning of observation.

X-ray examination revealed bilateral calcifications of the hilus and a thickening of the apical pleura with fibrous interstitial changes. No evidence of tumor in the lungs was found.

Spot radiography of the right leg below the knee and of the right upper arm showed no pathological changes.

Radiography of both optic canals was normal.

Examination of the blood: Wassermann and Kahn tests, negative. Erythrocytes, 4,300,000; hemaglobin, 82%; leukocytes, 5750. Leukocyte distribution: segmented cells, 55%; eosinophiles, 3%; monocytes, 6%; lymphocytes, 34%. Sedimentation rate, 30 mm. in an hour.

The urine tests were normal. Melanin and melanogen were not found in the urine.

No malignant cells were found after a sternal puncture.

The neurological, internal, and E. N. T. examinations gave no evidence of an extrabulbar tumor.

Ten days after the first examination, on Oct. 1, examination of the left ocular fundus showed the following changes: Optic disc ill defined. Upper third of the disc definitely hyperemic. The tumor was 2 D. D. in size. Its upper margin was poorly defined, while the lower, temporal, and nasal margins were rounded off. The tumor itself was of a dirty greyish-green color; its surface, uneven, with somewhat brighter reflexes, and it was elevated 1 D. The blood vessels not covered by the tumor were normal, except for one ampule-like distention of a small vessel, located at the 3 o'clock position. At an earlier examination this had appeared to be a hemorrhage. Temporal to the tumor, in the 1-3 o'clock area, a definite change in pigmentation was just visible.

Fig. 2.—Aspect of tumor three weeks later.

There had been no change in visual acuity from the previous examination.

Seventeen days after the first examination, on Oct. 7, the left eye showed that the mass had encroached on the upper temporal margin of the disc and further. One could clearly see the extension of the tumor out and downwards. Near the temporal vein and just beneath the disc were two small islands of pigment. The surrounding area of the optic disc was slightly swollen.

The tuberculin tests with threefold and fourfold dilutions of old tuberculin were negative. After the injection a slight clouding of the posterior parts of the vitreous body was noticed.

The field of vision showed a further extension of the blind spot. Visual acuity was 0.2.

On Oct. 16 the tumor had spread over three-quarters of the disc so that its only free parts were the upper nasal area from 10 to 1 o'clock. Even this area showed hyperemia and edema (Fig. 2).

By Oct. 22 the neoplasm had spread over the whole disc, being of a brown-grey-green color and 2 D. D. in size. The surface of the tumor was uneven, showing a network of small blood vessels. The lower vessels of the retina were completely covered by the neoplasm, while the upper ones could only be seen at the margin of the disc. Near the upper temporal vein, ½ D. D. away from the disc one could discern a poorly defined island of pigment, ¼ D. D. in size. Near the lower temporal vein one could discern another two or three such islands.

Visual acuity at this time was 0.2.

The eye was enucleated on Oct. 24. The operative and postoperative course were both normal.

The enucleated globe was cut in half in the vertical plane. Serial paraffin sections were stained with hematoxylin and eosin and were studied from the nasal margin of the disc to the temporal one. On the nasal

Fig. 3. — Section of nasal portion of optic disc.

Fig. 4.—Section of nasal portion of optic disc.

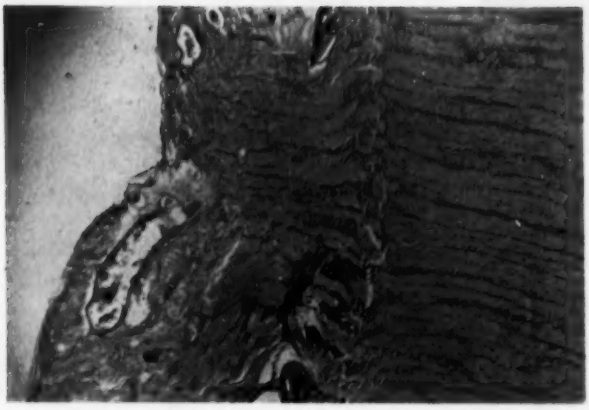


Fig. 5.—Section of nasal portion of optic disc.

side, the choroid was normal, while the outer layers of the retina were swollen and contained a number of macrophages. The layer of ganglion cells and nerve fibers was well preserved and showed cross sections of blood vessels (Fig. 3). There was no tumor substance at the nasal margin of the optic disc (Fig. 4).

Continuing with our serial sections we found that the elements of the pigmented tumor appeared in the lower third of the disc (Fig. 5). As we approached the central vessels, the pigmented elements of the tumor involved the lower half of the disc (Fig. 6). The surrounding choroid was normal. The tumor was so highly pigmented that it was impossible to differentiate the structure of cells. The greater part of the tumor was located over the lamina cribrosa, which at this level of the serial sections constituted a barrier passed by only an insignificant portion of the neoplasm. It extended right to the extrabulbar portion of the optic nerve, involving the area between the bundles of nerve fibers in the form of parallel lines (Fig. 6).

The tumor penetrated into the disc to a much greater extent and at its inferior margin into the surrounding retina. In the latter the tumor involved the outer layers but did not damage the ganglion-cell layer or the layer of nerve fibers. In the retina the pigmented elements were chiefly located around the blood vessels. If not considered as a part of the series, one section of the tumor would give the impression of a pri-

Fig. 6.—Optic disc in the area of the central blood vessels.

Fig. 7.—Section of temporal portion of the optic disc.

Fig. 8.—Section of temporal portion of the optic disc.

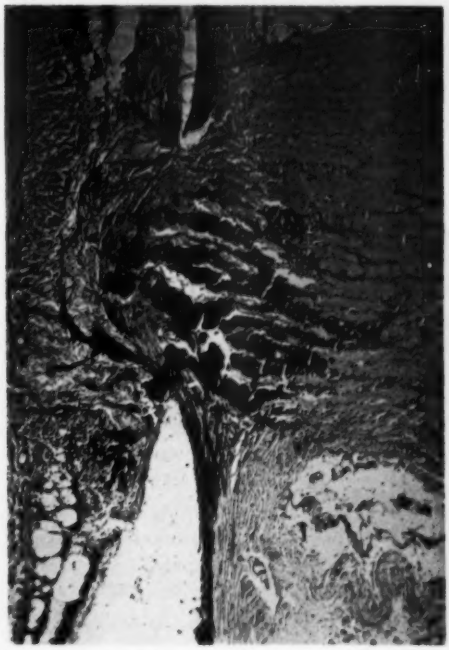
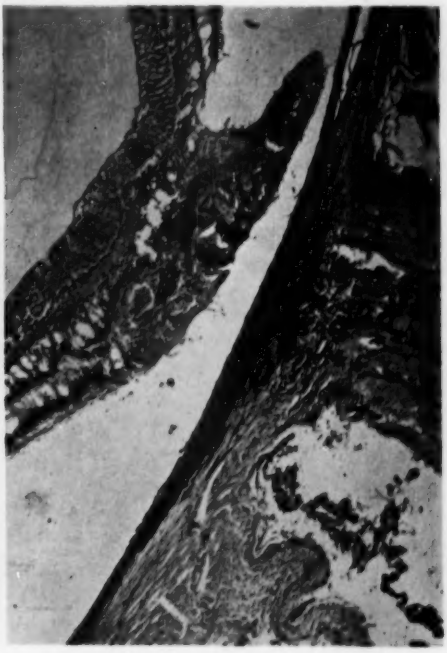


Fig. 9.—Section of temporal portion of the optic disc.



mary pigmented tumor of the disc (Fig. 6). Toward the temporal margin of the disc (Figs. 7 and 8) the tumor increasingly involved the disc but never reached its upper margin. Here the tumor penetrated the extrabulbar portion of the nerve more massively and in the form of parallel bands alone the fibrous partitions. In the retina the tumor considerably overlapped the lower margin of the disc, involving the outer layers, which in the locality showed signs of vacuolization. At this level of the serial sections the tumorous elements were located in the juxtapapillary portion of the choroid as well as in the lower parts. This contrasted with the region above the disc, where the choroid was normal. Circumventing the margin of Bruch's membrane, this tumor was directly connected with the portion on the optic disc and retina (Figs. 7 and 8).

From the serial sections at the temporal margin of the disc it was evident that the tumor extended further into the choroid, both temporally and beneath the disc. Outside the choroid (the detachment occurred in the course of making the histologic specimens) one can see the pigmented mass in the outer layers of the retina overlapping the margin of the disc temporally (Figs. 8 and 9).

Finally, the end of the series showed the termination of the tumor in the temporal area of the disc (Fig. 10).

The cellular structure of the tumor only became visible after the pigment had been removed (by Mawas' method). The tumor cells had a round or oval nucleus without major atypical features, while the chromatin was distributed in the form of a network. There was a fair amount of protoplasm, slightly stained after depigmentation (Figs. 11 and 12). The cells could be found in all parts of the tumor (disc, choroid, extrabulbar portion of the nerve, and retina). In places they were distributed in the form of whirls. This aspect and distribution of tumor cells can likewise be seen in certain malignant melanomas of the choroid (meningoblastoma[9]). However, the pigment was not located exclusively inside the tumor cells but to a large extent in the macrophages, in the disc and retina. After depigmentation these macrophages could be seen as the outline of cells whose completely flattened nuclei had pushed towards the peripheral zone; the large empty space is where the pigment was located in the cytoplasm.

Comment

The patient was sent to the clinic by the neurologist for examination of the ocular fundus, in order to establish the cause of the headaches. She herself did not complain of any trouble with her eyes. She had not noticed the low visual acuity, which re-

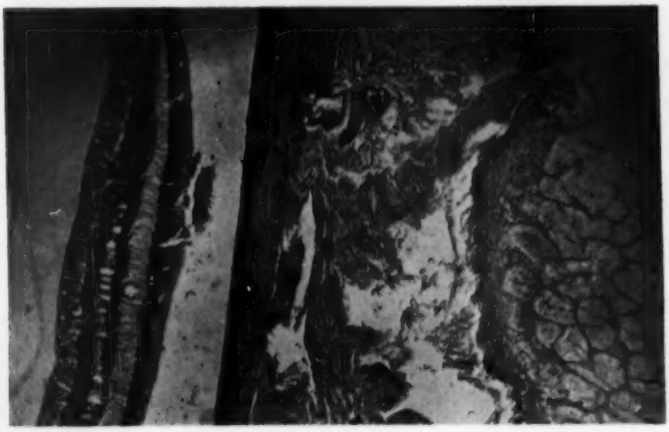


Fig. 10.—Section of temporal portion of the optic disc.

Fig. 11. — Aspect of tumor after depigmentation.

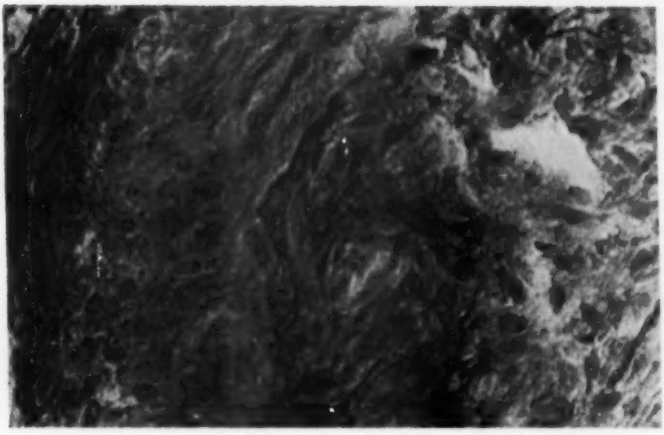


Fig. 12. — Aspect of tumor after depigmentation.

mained almost unchanged throughout her illness. At the first examination the changes in the fundus pointed towards the diagnosis of a neoplasm of the optic disc, and this was confirmed in the course of later examinations, with eventual histologic corroboration. The appearance of the growth as well as the other findings ruled out tuberculoma, gumma, cyst, drusen, etc.

The possibility of a metastatic neoplasm was excluded so far as possible by a general examination. The aspect of the tumor itself spoke against a phacomatosis, as did the absence of changes in the retina and other organs. We therefore came to the conclusion that it must be a primary tumor of the optic disc or a secondary tumor originating from the surrounding tissue. The actual appearance of the growth gave the impression that it was a pigmented neoplasm; according to its localization on the disc, most probably a primary tumor of the latter.

In view of our histopathological findings in the serial sections of the tumor, the study of an unbroken histological series of sections of the whole disc and its surrounding tissue was essential to establish the origin and nature of the papillary tumor. This manner of examination revealed that the major portion of the tumor was located in the disc itself, that it penetrated to a slight degree through the lamina cribrosa into the extrabulbar portion of the nerve, and that it extended considerably into the outer layers

of retina, beneath and temporally from the disc. Serial sections likewise showed that the tumor on the disc and retina was in direct communication with a tumor in the juxtapapillary choroid. The depigmented sections showed the histological structure of the growth to be similar to that seen in certain malignant melanomas of the choroid.

Clinically the tumor appeared to be a pigmented primary tumor of the optic disc, while it only became clear after serial histological sectioning that part of it was located in the choroid as well. The fact that the tumor existed in the choroid considerably undermined the opinion that it was a primary pigmented tumor of the disc, especially since pigmented tumors of the choroid are common, whereas those on the disc are extremely rare (or nonexistent). The structure of the tumor likewise spoke in favor of the choroidal origin of the neoplasm.

Conclusion

Clinically the tumor described gave a strong impression of being a primary tumor of the optic disc. Histologic sections of the nasal half of the disc were likewise compatible with such a conclusion. However, sections of the temporal half and margin of the disc revealed the part played by the choroid in the process of the pigmented neoplasm, which histologically corresponded to certain species of malignant melanoma of the choroid.

Our case proves that the origin of primary tumors of the optic disc can only be established if the clinical findings are followed up by careful histologic studies.

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REFERENCES

1. Vazquez-Barrière, A.: Bemerkenswerter Fall von Melanosarkom der Papille, Klin. Monatsbl. Augenh. 49:43-48, 1911.

2. Oloff, R.: Über primäre Tumoren und tumorähnliche Bildungen der Papilla nervi optici, Klin. Monatsbl. Augenh. 55:313-325, 1915.

3. Oguchi, T.: Über einen Fall von Melanosarkom der Sehnervenpapille, von Graefes Arch. Ophth. 130:427-431, 1933.

4. Nordmann, J.: Tumeurs de la papille, in Bailliart, P., et al.: Traité d'ophthalmologie: Vol. 5. Pathologie, by Amsler et al., Paris, Masson & Cie, 1939, pp. 725-734.

5. Duke-Elder, S. W.: Neuro-Ectodermal Tumours, in Text Book of Ophthalmology, Vol. 3, St. Louis, The C. V. Mosby Company, 1941, pp. 3095-3098.

6. Reese, A.: Benign and Malignant Melanoma of the Disc, in Tumors of the Eye, New York, Paul B. Hoeber, Inc., 1951, pp. 309-315.

7. Friedenwald, J. S., et al: Ophthalmic Pathology: An Atlas and Textbook, Philadelphia, W. B. Saunders Company, 1952.

8. deVeer, J. A.: Juxtapapillary Malignant Melanoma of the Choroid and So-Called Malignant Melanoma of the Optic Disc: A Pathologic Study, A. M. A. Arch. Ophth. 51: 147-160, 1954.

9. Mawas, J.: Personal communication to the authors.

10. Cordes, F. C., and Hogan, M. J.: Primary Malignant Melanoma of the Optic Disc: Report of a Case, Am. J. Ophth. 32:1037-1047, 1949.

Office Management of Glaucoma

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The office management of a disease such as glaucoma offers a formidable challenge. Therapeutic nimbleness must be based upon sound knowledge and continued perusal of the literature.

The phasic variation in ocular tension and the facility of aqueous outflow should be determined, and all glaucomatous eyes should be periodically subjected to perimetric study, ophthalmoscopic and slit lamp examination, refraction, gonioscopy, and measurement of the intraocular pressure.

Phasic Variations in Ocular Tension

A rhythmic diurnal variation in ocular tension is characteristic of the individual and occurs in a definite pattern which is the same in both eyes. It is independent of sleeping and eating habits, rest, work, blood pressure, age, sex, refractive error, and width of chamber angle.

This oscillation in tension is made up of a descending and an ascending phase. A diurnal fluctuation of 5.0 mm. Hg Schiøtz is rarely exceeded in the eye of a normal person. In general, a tension rise in a nonglaucomatous eye occurs in the early morning, followed by a gradual fall.

Regular rhythmic but exaggerated variations of ocular tension occur in glaucomatous eyes. Duke-Elder pointed out that the phasic variation of tension in simple glaucoma may be divided into three groups.

1. The falling type makes up about 20% of cases. The tension is high early in the morning, reaching a peak soon after the person awakens. A gradual fall then occurs, with a low at about midnight.

2. A rising type comprises some 25% of cases. The tension in this type is low in the early morning, gradually increasing until a peak is reached about 4 to 6 p. m. A steady fall then occurs during the evening and night.

3. A double-variation type may be demonstrated in nearly 55% of cases. The tension rises in the morning, reaching a peak about 9 a. m., then falls to reach a minimum early in the afternoon. A secondary rise next occurs, reaching a maximum at about 6 p. m. This is followed by a fall during the night, succeeded by a gradual rise toward morning.

Congestive glaucoma has but one type of phasic variation. This is characterized by a peak of tension in the evening hours and a fall during sleep.

The type of phasic variation may be ascertained by discontinuing the use of miotics for 48 hours, after which the same observer determines the tension with the same tonometer at two-hour intervals. The period between 11 p. m. and 5 a. m. is relatively unimportant as far as phasic variation is concerned; so during that time the patient may be given a rest from the tonometric measurements.

In this way valuable information may be obtained not only in a diagnostic sense but also from a therapeutic standpoint. Thus it is ascertained at what time of day the use of miotics is indicated. For example, a patient with a falling type of variation requires miotics during the early morning hours. A patient with a rising type requires miotic therapy in the late afternoon and early evening, and the patient with a double variation in diurnal tension needs early morning and late afternoon miosis.

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The references for this paper may be obtained from the author on request.

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Tonography

Tonography is a new and useful adjunct to the management of glaucoma. This procedure is helpful in the diagnosis of the disease, in following the course of medical treatment, and in the evaluation of surgical procedures.

The footplate of a Mueller electric tonometer is allowed to rest continuously for four minutes on the anesthetized cornea. Fluctuations in the intraocular pressure may be recorded directly as read from the tonometer or registered on the tape of a recording device.

The facility with which the aqueous is expressed from the eye is designated by the coefficient C. Becker, using the 1955 tonometer calibration scale of Friedenwald, found the normal value of C to vary from 0.2 to 0.6, with a mean of 0.33 cu.mm/minute/mm. Hg of pressure. Spencer, Helmick, and Scheie found an average variation of ±0.04 cu.mm/minute/mm. Hg, or a ±19% from the mean C.

The flow (F) values for normal and glaucomatous eyes, according to Becker, average 2.3 cu.mm/minute when calculated from the formula $F=(P_o-10)\times C$ when P_o=the initial intraocular pressure. Hypersecretion is believed to occur when the flow (F) is greater than 4.0 cu.mm/minute/mm.

Since there may be variation as great as 25% in tonometric readings taken on the same patient at different times of the day, and only 16.5% if taken at the same time of day, it is advisable that the tonographic procedure be performed at the same hour of the day. It is preferable that the studies be carried out in the early morning, when, according to Scheie, the physical and emotional activities are at a minimum. If the coefficient of aqueous outflow is borderline, certainly more than one tonography should be resorted to. An interval of more than five minutes should be allowed between the tonography of the right and the left eye. If such an interval is not allowed, the tonography of one eye has been shown to influence the aqueous outflow of the opposite eye.

Hypersecretion glaucoma presents an intermittent or persistent elevation of intraocular pressure in an eye with normal scleral rigidity, open angle, adequate facility of outflow, and a flow value greater than 4.0 cu.mm/minute. Field loss occurs and is proportionate to the degree and persistence of abnormal intraocular pressure.

Patients with open-angle glaucoma show as an early feature of their disease a decrease in the facility of aqueous outflow. The value of C improves as the intraocular pressure is normalized by the use of miotics. An impaired facility of outflow in spite of a normal intraocular pressure indicates a need for increasing the strength of miotics and the frequency of their administration.

A severely impaired C occurs during an attack of angle-closure glaucoma. The outflow returns to normal with a fall of intraocular pressure, unless peripheral anterior synechias have formed.

Water drinking tends to decrease the facility of outflow in glaucomatous eyes but has less effect on the outflow of normal eyes.

There is disagreement whether or not phasic variations in the intraocular pressure cause proportionate changes in the facility of aqueous outflow.

Campimetry

In the old and somewhat uncooperative patient, a confrontation field may offer the only reliable information obtainable. If lens opacities, extreme miosis, or marked refractive error is present, a target of 5 to 10 mm. may be necessary. Chandler believes that a 3 mm. object at 33 cm. or at 1 meter is small enough for most fields of vision.

If the patient is cooperative, and a general survey with larger targets has been carried out, then the use of small test objects adds to the refinement of the perimetric study.

Perimetry carried out while the tension is considerably elevated and before nerve-head changes have occurred may reveal field defects which disappear when the tension is normalized.

Scheie has found that the visual field is significantly reduced in size when the pupil is miotic. This occurred in presbyopic patients in whom accommodative spasm could not be a factor. He also found that ciliary spasm as well as nuclear lens opacities caused an apparent deterioration of the field. The combination of pupillary constriction and cataractous changes caused marked visual field change. Uncorrected high refractive errors also simulated defects in the field of an otherwise healthy eye.

One must, therefore, be mindful that visual field changes are inconstant, changing with the ocular tension, illumination, pupillary size, transparency of the media, and refractive state.

Follow-up visual field studies should be carried out as nearly as possible at the same time of day to offset the effect of diurnal variation in the tension. The pupils should be of constant size during subsequent field examinations. Illumination should be consistent, and high refractive errors should be corrected.

The sudden appearance of a disturbance in the 1/2000 isopter, causing baring of the blind spot, is the earliest field change indicating that the glaucoma is not perfectly controlled. Another extremely early field change is the small scotoma which can be isolated in the same isopter as the blind spot but separate from and usually above it. As the glaucoma progresses, this isolated scotoma lengthens and joins the blind spot to produce a typical Seidel scotoma. The appearance of a large sector defect is further evidence that the glaucomatous process has not been stayed. Posner and Schlossman have found that the sudden appearance of an arcuate scotoma in a previously normal half-field is a grave prognostic sign. Dunnington has pointed out that if an island of vision surrounding the point of fixation is all that remains and if that island is irregularly shaped, with its nasal border practically in contact with the point of fixation, any sudden reduction in pressure may result in a complete loss of central vision. A medical regimen is therefore best in this type of case.

Ophthalmoscopic Examination

The structures of the eye in the posterior segment should be described in detail before miotic therapy is initiated and periodically thereafter. A description of the fundus and a classification of the papilla are not as in a prognostic sense as are successive sketches and measurements. The need of periodic study of the eye grounds necessi- accurate nor as useful means of comparison tates the temporary discontinuance of the use of miotics, particularly if the miosis is marked and the media are hazy. Little difficulty ordinarily ensues during this therapeutic lapse, especially if the ocular tension is in the descending phase. If the angle is open, the pupil may ordinarily be dilated with impunity. A steamy cornea may be cleared enough for accurate ophthalmoscopic examination by gentle massage of its anesthetized surface with the rounded tip of a glass or plastic rod or by placing on the anesthetized cornea a highly hydroscopic collyrium such as hypertonic saline, glycerin, or carboxymethylcellulose in glycerin.

The appearance of optic disc pallor, change in excavation, and displacement and angulation of vessels on the papilla are all manifestations of uncontrolled glaucoma. Every effort should be made to avoid the development of such grave prognostic signs.

Biomicroscopy

Careful slit lamp study permits a more accurate classification of glaucoma and a better understanding and control of the disease. The presence of keratic precipitates and/or posterior synechias indicates that the glaucoma is secondary to iridocyclitis, whereas the finding of cells in the aqueous humor usually, but not always, suggests iridocyclitis as an etiologic factor. The cause of the glaucoma may be disclosed by finding anterior lens capsule exfoliation or by the presence of an intumescent cataract or a subluxated lens.

The slit lamp should be routinely used to estimate the depth of the anterior chamber. The acquisition of the habit of observing with a narrow beam the rate at which the iris approaches the most peripheral portion of the anterior chamber makes possible a fairly reliable determination of the width of the angle without actually seeing it.

Ascher's so-called aqueous veins may be observed in the bulbar conjunctiva of many eyes. They are best seen biomicroscopically under high power in the limbal and paralimbal region. Aqueous veins appear pale in contrast to the ordinary blood vessels, and each vein may be divided into as many as three or four layers of blood and clear fluid. They tend to run in a straight line to empty into a recipient vessel.

The aqueous veins react characteristically to phases in ocular tension. In the ascending phase there is little or no flow of aqueous through the aqueous veins. The flow is average when the tension is level, no matter what its height, and is greatly increased in a descending phase of tension. If the recipient vessel of an aqueous vein is compressed, a blood influx is usual in the ascending phase and an aqueous reflux is common in the descending phase.

Refraction

A change in refractive error often occurs after the tension is normalized either medically or surgically. A reduction in hyperopia or an increase in myopia frequently occurs. This is especially true with the use of miotics, inasmuch as drugs which induce miosis also stimulate accommodation. It is imperative, therefore, that periodic refractions be done. By this means the progress of the disease may be followed and the patient's vision and comfort kept at a maximum, with a resultant continuing high plane of morale.

The refraction should be done while the eyes are under the influence of the drug which best controls the tension. It is wise to refract the patient at a time when it is customary for him to use his eyes most. In this way a peak of optical performance can be obtained. The prescribing of absorptive lenses should be avoided if the angle is narrow, and any tendency for overaccommodation should be nullified by a proper correction. A refraction should be avoided after tonometric measurement or if the patient is fatigued from field studies or indisposed for any other reason.

A functional failure of the ciliary muscle is prone to accompany a high intraocular pressure. Prescriptions for glasses, therefore, should not be based on measurements made while the ocular tension is elevated.

Gonioscopy

Gonioscopic examination of all patients with glaucoma should be made as soon as the disease is detected and periodically thereafter. Gonioscopy should be done prior to surgery to gain information as to the type and site of operation. Postoperative gonioscopy discloses the presence of goniosynechia and permits intraocular inspection of the area of operation. The knowledge gained thereby enables a better forecasting of the success of the operative intervention.

If the angle is found to be open, and if it does not close with a tension rise, the patient need not avoid dark rooms or excitement, may wear dark glasses, and may submit to pupillary dilation, if necessary, without fear of precipitating an acute rise in tension. Because the open-angle type of glaucoma is particularly resistant to surgery, a medical regimen is preferred. This should be continued unless the base pressure reaches a level of 35 mm. of mercury or the fields show continuing deterioration.

Angle-closure glaucoma before peripheral anterior synechia formation occurs responds remarkably well to miotics. Inasmuch, however, as peripheral anterior synechias frequently form and contraindicate the continuation of medical therapy, and since surgery is highly successful in this type, early operative intervention should be urged.

Tonometry

Once the type of phasic variation in ocular tension is determined and miotic therapy is instituted, tonometric measurements should be taken at the time of peak pressure in order to ascertain the effectiveness of the medication. The intraocular pressure must be recorded periodically after the type, strength, and frequency of drug administration has been determined. A record must be made which includes the patient's name, date, time of day, weight used, tension, size of pupil, strength of medication, and frequency and time of last administration of the drug. As nearly as possible, the same person should take the tension readings and with the same tonometer.

Scleral rigidity should be considered in patients who show continuing adverse field changes in spite of seemingly adequate control of tension. The ocular rigidity is abnormally low if the readings with the 10 gm. weight consistently indicate a lower tension by 2 mm. or more than do the readings with the 5.5 gm. weight. The intraocular pressure, because of low scleral rigidity, is therefore higher than indicated by either of the plunger loads. If the scleral rigidity is found to be low the therapy must be adjusted accordingly.

Each morning and evening the tonometer must be taken apart and cleansed with 95% alcohol. It should then be carefully dried with cotton, and its barrel, with a pipe cleaner. The reassembled tonometer should rest during the day in a stand a short distance above an unlighted alcohol lamp. Dreisler has shown that flaming the tonometer footplate kills non-spore-bearing bacteria in 10 seconds. The instrument is allowed to cool for one minute before it is used. Flaming does not damage a stainless steel tonometer.

A standardized tonometer is essential, and it should be regularly restandardized or at least periodically compared in its measurements with other tonometers in the office.

The Miotics

Pilocarpine.—The most universally used miotic is pilocarpine. Allergic reaction or irritation by the drug is rare, and tolerance develops slowly. Pilocarpine is a vasodilator, and, because of this, a small rise in tension occurs after instillation followed by a more prolonged fall in tension. Pilocarpine, as far as it is known, acts directly on the smooth muscle cell. It behaves like the choline derivatives, the important difference being that it is stable and not destroyed by cholinesterase. A miosis is produced beginning 10 minutes after instillation and persisting for about 24 hours. The therapeutic effect is good for four hours. The stimulation to accommodation is mild and is proportionately less than the induced miosis. The refractive error is therefore disturbed very little by a weak solution of the drug. Accommodative spasm disappears in about two hours. The physiologic activity and absorption of the drug is better in alkaline solution, but stability is greater when the pH is kept between 5 and 6.5.

Pilocarpine may be prescribed in sodium acid phosphate and disodium phosphate buffer. If benzalkonium chloride is added as a wetting and sterilizing agent, the hydrochloride salt must be used. Neither pilocarpine nitrate nor the Gifford buffer can be used, because of their incompatibility with benzalkonium chloride. Recent evidence indicates that chlorobutanol is a better preservative than benzalkonium chloride alone. Riegelman, Vaughn, and Okumoto combined polymyxin B sulfate and benzalkonium chloride as a chemical preservative, the former because of its action against strains of Pseudomonas aeruginosa and the latter because of its rapid action against Gram-positive organisms. A consistent absorption can be obtained by placing pilocarpine in a 0.5% to 1% methylcellulose solution (4000 centipoise type).

The solution strength may be varied from 0.25% to 10%. A 1% solution is usually ordered, particularly if the initial tension is under 40 mm. Hg. As a rule, if a 2%

solution fails to control tension, surgery or a change to some other miotic or combination of drugs is indicated.

Physostigmine (Eserine).—This miotic drug exerts its effect by inactivating cholinesterase. It produces a rapid intense miosis. The iris becomes hyperexcitable, and so painful spasm may occur when the patient passes from darkness into light. The accommodation is abruptly and severely stimulated, and so cyclospasm occurs upon an attempt at close work. The tonus of the skeletal muscles in the region of the eye is increased, and, as a result, annoying diffusion of proteins arises, causing a primary transient increase in intraocular pressure. This increased pressure is very soon blepharospasm takes place. Physostigmine is a vasodilator and, as a result, an increased offset by the miotic effect. Long-continued use of physostigmine frequently causes a follicular conjunctivitis. It is believed that this is due to the chronic irritation produced by the end-products of the deterioration and degradation of the drug. Physostigmine in ointment form infrequently produces a local reaction. Dissolving small amounts of cocaine in a physostigmine solution or placing the drug in an oily vehicle such as castor oil, using the alkaloid of physostigmine, is said to reduce the incidence of irritation. Physostigmine may be prescribed in a solution of boric acid, sodium bisulfite, and benzalkonium chloride. The sodium acid phosphate, disodium phosphate buffer of Hind and Goyan should not be used, because its pH is near 6.8, and at this pH physostigmine produces a most irritating sensation. Boric acid retards the rapid neutralization of a solution and maintains the physostigmine solution at a pH below 5. At this pH the irritating effect of physostigmine is largely eliminated. The addition of bisulfite prevents physostigmine solution from changing to a pink color. Benzalkonium chloride acts as a wetting and sterilizing agent, but, because it is incompatible with the salicylate radical, the sulfate salt must be used. Benzalkonium chloride may be combined with polymyxin B sulfate, or chlorobutanol may be substituted as a preservative. Physostigmine is prescribed in solutions of 0.2% to 0.5%. Physostigmine is chiefly indicated in cases where there is reason to temporarily defer an operation or in an attempt to lower the tension from a high level. An eye that requires physostigmine to control the tension needs surgery.

Neostigmine (Prostigmin).—Neostigmine is a synthetic carbamate alkaloid which has the same cholinesterase-inhibiting action as physostigmine. The two drugs are about equal in effect, but neostigmine can be used in more than twice the concentration of physostigmine without producing irritation. Neostigmine bromide, 5%, is supplied by the manufacturer in 1% boric acid solution. It may be diluted by adding boric acid solution to produce a lesser concentration. Neostigmine is usually prescribed in a 3% to 5% solution.

Carbachol U. S. P. (Carbamylcholine Chloride; Carcholin, Doryl).—Carbachol is a potent toxic choline ester which has the advantage of not being destroyed by cholinesterase. This drug has a double action, not only stimulating the motor endplate of the muscle cell, as do all the choline substances, but also inhibiting to some extent the action of cholinesterase. Its action is therefore not augmented by the use of neostigmine or physostigmine.

Carbachol is not only more powerful than mecholyl but has a more prolonged action. Accommodation is definitely stimulated by the drug. It is more effective and longer-lasting than a 2% solution of pilocarpine. It, however, at the height of its activity, does not constrict the pupil as much as does pilocarpine and therefore causes less blurring. It is best used as a rest drug, particularly in eyes which have become irritated by or in which resistance to pilocarpine has developed, or it may be employed in those eyes in which 2% pilocarpine falls just short of controlling the tension. It rarely produces sensitivity, but resistance to the drug does develop. The drug has a prolonged

action, lasting as long as 8 to 12 hours. It is therefore effective if used only two to three times daily.

Carbachol is best prescribed as a 1.5% solution in 1:3000 benzalkonium chloride solution or as 1.5% ointment, suspending 0.5 gm. of the active ingredient in 33 gm. of petrolatum U. S. P. The patient should be advised that the ointment has been properly placed in the eye if the vision is blurred for a short time after its use.

Methacholine Chloride U. S. P. (Acetyl-β-methylcholine Chloride; Mecholyl Chloride).—Methacholine chloride is a synthetic choline derivative which is readily destroyed by cholinesterase and should therefore be prescribed with one of the cholinesterase inhibitors such as neostigmine. The drug is a direct stimulatory miotic, producing its specific effect on the effector cells supplied by the parasympathetic nervous system. It stimulates accommodation, is a vasodilator, and is poorly absorbed through the cornea. Methacholine has very little effect on the normal pupil in less than 15% solution. It does, however, constrict the pupil of a glaucomatous eye in a 10% solution. The miosis produced is brief, persisting for about two hours. The action of methacholine is so rapidly terminated by cholinesterase that systemic effects seldom follow even repeated instillations of the drug. Its penetration may be increased by the use of a wetting agent such as benzalkonium chloride, by corneal massage, or by preceding the use of the drug with a drop of 0.5% tetracaine hydrochloride. It is most effectively administered by iontophoresis. Retrobulbar injection of methacholine has been reported as producing near fatalities. It is usually prescribed in a 20%, 1:3000 benzalkonium chloride solution to be used in combination with neostigmine. Methacholine is particularly effective in angle-closure glaucoma in the acute congestive phase.

Isoflurophate (DFP).—This powerful miotic has been used in the treatment of glaucoma since 1946. It produces its effect by destroying or combining with cholinesterase. Isoflurophate is more effective and prolonged in action than is physostigmine or neostigmine. The induced miosis may last as long as 27 days. The drug is a vasodilator and may produce unpleasant symptoms because of its strong cyclotonic effect. Ciliary spasm may be minimized by a preliminary instillation of a more concentrated preparation of isoflurophate than is to be subsequently used. Detachment of the retina, activation of a quiescent uveitis, and the production of iris cysts have followed its use. The precipitation of an acute attack has been noted following the use of isoflurophate in angle-closure glaucoma. It is particularly effective in the treatment of aphakic glaucoma.

Isoflurophate forms hydrofluoric acid with water. It is therefore used in anhydrous peanut oil. It is supplied by the manufacturer in 0.1% concentration. It may, however, be further diluted with peanut oil in an effort to find a suitable concentration for the individual case. Care must be taken not to contaminate the dropper with tears, inasmuch as any water introduced into the bottle containing the miotic will greatly reduce the concentration of isoflurophate.

Combination of Miotics

The combination of a vasoconstrictor drug, such as phenylephrine (Neo-Synephrine) hydrochloride 1% or epinephrine (Adrenalin) 1:1000, with miotic drugs producing vasodilation and cyclotonia, such as pilocarpine, physostigmine, and isoflurophate, has been advocated in cases of angle-closure glaucoma. Such a combination often causes the intraocular pressure to drop from 10 to 15 mm. Hg below the level obtained by a miotic alone.

The action of methacholine chloride is rapidly terminated by cholinesterase, and therefore its effect may be enhanced and prolonged by combining its use with that of neostigmine. Swan, however, felt that if the iris muscle is reactive either methacholine or neostigmine alone is sufficiently potent

and that if the muscle is badly damaged the miotic combination is ineffective.

Lowenstein and Lowenstein found that the combined administration of pilocarpine and physostigmine is more effective than the use of either drug alone. They believe the effect is additive and not competitive. Swan and Gehrsitz, however, have found that pilocarpine decreases the reactivity of the iris sphincter of the albino rabbit to the subsequent action of physostigmine, isoflurophate, and physiologically produced acetylcholine. They suggest that pilocarpine competes with acetylcholine for the receptor mechanism of the iris sphincter. It is therefore debatable whether or not to combine the use of pilocarpine and physostigmine.

The hyperactivity of the intraocular muscles induced by physostigmine and isoflurophate is undesirable in the necessary continued treatment of chronic glaucoma. The spastic action induced by either of these drugs may be minimized by the preliminary administration of pilocarpine.

Leopold and MacDonald have observed that the sensitivity of the pupil to isoflurophate is decreased by the prior instillation of physostigmine. Conversely, the pupil exhibits a long-lasting increased sensitivity if the administration on physostigmine is preceded by the instillation of isoflurophate. It is believed that physostigmine prevents the action of isofluorphate by protecting the cholinesterase from isoflurophate.

Acetazolamide

A carbonic anhydrase inhibitor, acetazolamide (Diamox), was developed by Roblin and his associates in 1950. Becker reasoned that this same carbonic anhydrase inhibitor, which had proved to have remarkable diuretic properties, might inhibit the formation of bicarbonate ions on the part of the ciliary body and thus reduce aqueous production. Subsequent observation showed this to be true, the average suppression of the secretion being about 60%.

That the reduction in intraocular pressure was not due to the diuretic action of the drug was demonstrated by noting that acetazolamide reduced the tension of the eye in nephrectomized rabbits. Proof that the induced hypotensiveness of the eye was due to a decrease in the rate of aqueous inflow, and not to an increase in the facility of outflow, was shown by tonographic studies. This assumption was also verified by observing that the appearance-time of fluorescein in the aqueous after intravenous injection was increased nearly twofold by the administration of acetazolamide.

Acetazolamide is rapidly metabolized and excreted in the urine. Although closely related to sulfanilamide, it has no antibiotic effect and does not embarrass pulmonary carbon dioxide discharge. Large amounts of carbonic anhydrase are present in the retina, lens, and ciliary body, but its inhibition by acetazolamide is not absolute, and the ocular tissues are therefore not impaired.

Acetazolamide damps the phasic variation in intraocular pressure and reduces the fluctuation induced by the water-drinking provocative test to a near-normal pressure curve.

The systemic side-effects produced by acetazolamide are neither alarming nor serious. Nearly all patients experience paresthesia of the hands and feet. This is usually well tolerated but may be alleviated by the administration of potassium chloride, 1 to 2 gm. three times a day. Loss of appetite occurs in about one-half of the patients taking the drug. If a normal food intake is continued in spite of anorexia, the appetite returns. Excessive fatigue is prone to occur in the aged, and drowsiness is particularly troublesome. Urinary calculi may fragment and dislodge and cause ureteral symptoms as the urine pH is changed from acid to alkaline. Hearing loss, dermatitis, disorientation, and leukopenia have been reported as occurring occasionally. A few patients (6%, Becker) have responded initially to acetazolamide and then have developed a resistance to the drug. The reason for this intolerance is not understood. Occasionally

a patient will respond to acetazolamide when it is administered intramuscularly, but not when it is given orally.

After an oral dose of acetazolamide the intraocular pressure of the responsive eye begins to fall in about one to two hours and reaches a low in about three to five hours. It is believed that the suppression of aqueous flow lasts much longer than the depression in intraocular pressure. The return to normal pressure in 6 to 24 hours is thought to be due to an increase in outflow resistance.

Inadequate control of the intraocular pressure may result from failure to co-administer miotics or because of the development of a refractory state due to infrequent small dosage of the drug. Friedenwald believes that a "refractory state is one of mild acidosis, the drug being administered at suboptimal dose frequency." A state of continued efficacy of the drug is obtained by an increased frequency of administration, causing a more marked acidosis. Unresponsiveness (pseudoresistance) of the occasional patient to acetazolamide may represent the ability of the eye to maintain the intraocular pressure by a compensatory decrease in the outflow to offset the decreased inflow. The administration of adrenal steroids, such as fludrocortisone, prevents such a compensatory decrease in the facility of aqueous outflow in the eyes of unresponsive rabbits. When the human eye is resistant to treatment initially or when resistance develops during the course of treatment, this steroid may prove to be of value in causing response to therapy.

Acetazolamide buffers episodes of hypersecretion and prevents further field loss in hypersecretion glaucoma.

Acetazolamide may be given in amounts varying from 125 to 500 mg. orally each six hours. The average dose is 125 to 250 mg. every 6 hours or 125 mg. of regular and 125 mg. of delayed-action drug every 12 hours.

Acetazolamide may be administered for a year or more without any untoward effects. Its action may be potentiated by the oral administration of ammonium chloride, 1 to 2 gm. every six hours.

Other Therapeutic Measures

The retrobulbar injection of procaine, epinephrine, and hyaluronidase often will reduce the intraocular pressure to such an extent that miotics will then become effective and control the tension until surgical intervention can be safely accomplished. Ethyl alcohol in 50% to 95% strength may be injected retrobulbarly without fear of damage to the optic nerve. The injection of alcohol should be preceded by an injection of procaine. A transitory extraocular muscle paresis may ensue. Pain is abolished over a long period. The tension is often sufficiently lowered to permit the action of previously ineffective miotics or to enable one to go ahead and operate with greater safety. The tension is supposedly lowered because vascular axon reflexes are abolished, and since the axon reflexes are cut off as far as the other eye is concerned, a sympathetic rise in ocular tension of the fellow eye may be averted. There is no reason why retrobulbar injections can not be done in the office if a sterile technique is employed. Intravenous injection of hypertonic solutions, particularly sorbitol, aids in the control of tension. It is more advantageously and safely employed in cases that are hospitalized.

Rest must be insisted upon, and attention should be given to the fluid balance. A reduction of fluid intake should be recommended; particularly, the ingestion of large amounts of fluid within a short time should be discouraged. The avoidance of excitement and worry is important.

Office Procedure

The patient must be thoroughly acquainted with his or her condition, impressed with the necessity of following instructions explicitly and with the need of return visits at stated intervals. Written instructions to the patient act as a refresher to his memory and as a guide to relatives or persons

interested in helping the patient control his glaucoma.

If the patient can maintain with medicine a base pressure under 25 mm. Schiøtz and a diurnal variation under 5 mm. Hg and show no deterioration in the central fields, then a medical regimen may be continued indefinitely.

The medicine of choice should be the weakest, least irritating miotic which will control the tension with the smallest number of instillations. The miotic should be instilled one hour before the rise or rises which occur in the previously determined phasic variations in ocular tension. Acetazolamide may be added to the therapeutic routine of the average patient for months and even years without untoward effect.

Surgical intervention should be avoided in the aged, frail, or seriously ill patient; it should, however, be urged particularly if the glaucoma can not be controlled without frequent strong medication, is of angle-closure type, or if the patient has a life expectancy of 20 to 30 years or more.

Office records of patients with glaucoma must be carefully kept. It is a good plan to stamp a large red star-shaped figure in one of the upper corners of each glaucoma record to indicate to the person who is to handle the patient that this person should be cared for differently than the average office patient. Notation of the type of therapy in red ink on the record calls attention to various therapeutic measures that have been tried. The use of tension curves will enable the physician to see at a glance how the tension has been maintained over a long period of time. The tension-curve chart should also reveal the date and time of day each tension check was made, the weight used, size of pupil, medication employed, strength and frequency of the drug, and the dates on which the fields of vision have been checked and gonioscopy, tonography, and refraction done. Also on the tension curve sheet the value of C should be typed together with the time of day that the peak or peaks in the diurnal variation occur. Charts recording fields of vision should be properly labeled and clamped together.

Once the tension is stabilized, the patient should be seen in the office at regular intervals of from one to three months, depending upon the control of the glaucoma and the personal desires of the patient. Fields of vision should be determined every six months, and a refraction should be done at least every six months. If the glaucoma is of open-angle type, the pupils should be dilated at least once a year to offset the development of synechias and to observe the lenses and nerve heads. The office records should be completely reviewed at least yearly. It must be borne in mind that most elderly patients develop lens opacities because of their age and as a complication of their disease. Cataract extraction may greatly improve the vision in one whose continued visual decline was thought to be based entirely on progression of glaucoma.

Forty-Fourth and Farnam St. (31).

The Phosphene of Quick Eye Motion

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Entoptic imagery, which refers to reproducible visible phenomena arising within the human eye, is not a neglected subject. With Purkinje [9,10] it was a major field of investigation; his fiery rings are related to the present study, but he did not describe the present phenomenon proper. Helmholtz [5] mentions the phosphene of quick eye motion and pictures it, but he also fails to discuss it adequately. Duke-Elder [3] has a chapter on entoptic phenomena, but it does not include the eye-movement phosphene. Adler [1] devotes nine pages to entoptic imagery and does not mention the phenomenon. The closest recent approach to the present description is given by Friedman,[4] who states that in the dark the effects of optic nerve traction are recognized as the fiery rings of Purkinje. The circles include within their arc the blind spot.

Modern abstract journals list from 5 to 30 papers per year dealing with entoptic phenomena. One would expect the present observations, which are concerned with the phosphene from quick eye movement, to have been anticipated many times over. But to my knowledge this specific phenomenon has been described only incompletely by Purkinje and Helmholtz and later by Friedman.

Moore [7] describes subjective "lightning streaks," observed by 26 of his patients, 21 of whom were females with an average age of 63. The lightning streaks usually appeared in the temporal visual field, extended vertically, and were said to flash on and off periodically for a split second. Moore ascribed the lightning streaks to cystic retinopathy. Verhoeff [12] has given an authoritative discussion of Moore's lightning streaks, in which he points out that their occurrence is correlated with the development of a crop of opacities in the vitreous. The flashes thus do not imply any serious disease of the eye either at the time or subsequently. To evoke the flashes ocular motion is needed, whereby the shrunken vitreous exerts traction on the retina. Berens et al.[2] have also dealt with this subject.

I believe the eye-movement phosphene of the healthy eye to be mechanically related to, but definitely distinct from, Moore's flashes. It has a regular, highly organized pattern which can be reproduced at will. It is consistent for a given observer and closely similar in different observers. The position of the pattern in the visual field can be designated, and its size can be roughly measured. The present phosphene is a normal phenomenon, but it may be commonest during a particular age range; for, only one of the present observers remembers to have first seen it when he was 23. All the currently successful observers are now over 40.

Observations

From an inquiry among about 100 colleagues, near by and distant, I received answers in writing from 39. Of these, six besides myself were able to observe the present phenomenon with ease and in detail. Their observations agree with my own, within certain limits, on all important points. Unfortunately not all of the "successful" colleagues can be prevailed upon to sacrifice repeatedly their predawn morning hours.

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Division of Biological and Medical Research, Argonne National Laboratory.

Phosphenes are impressions registered by the retina but originating within the eye itself.

Most of the "unsuccessful" observers are credited with sincere and repeated attempts. Their failure to observe the phenomenon is ascribed to anatomical, possibly inherited, differences to be mentioned in the discussion.

The Phenomenon as Experienced by Me

The "flick phosphene" is best observed in the dark-adapted well-rested eye, i. e., before dawn after a restful sleep. Then if one flicks * the eyes, e. g., from left to right, with the lids closed, one observes in each monocular field the short-lived appearance of a bright pattern. The general shape of this figure is shown in Figure 1. In every observation the small end of the sheaf-like pattern points in the direction of the sudden eye movement, or flick. Each eye produces its own phosphene. With a flick directed horizontally to the left, the figure in the right eye is larger and brighter than that in the left eye.

* What is meant is a rapid motion, which can start from the rest position or from any position moderately off-center but away from that of the intended voluntary eye movement. The word "flick" has the proper connotation and is brief.

The phosphenes seen simultaneously in the two eyes are two separate images. Even though the monocular fields are fused, the images remain separate, since they are in the temporal quadrants. The sheaf-patterns could be superimposed if the observer showed marked exophoria. I have mild exophoria, which should tend to exaggerate the apparent distances between the sheaves. My own exophoria can be detected entoptically in the relaxed eye with closed lids. It appears to be overcome by sudden voluntary eye motion.

L. E. Lipetz suggested to me that I could "mark" individual eyes by briefly exposing one eye to a (fixated) light-source of moderate intensity. This labels the fovea, and the afterimage lasts long enough to allow two or three accurate entoptic observations. Both foveas can be marked to reveal any exophoria. All statements below regarding localization of the phosphenes with respect to the fovea are based upon such markings.

The color of the figures is a bright whitish with a slight admixture of blue or orange on a background of darkness. The sheaves

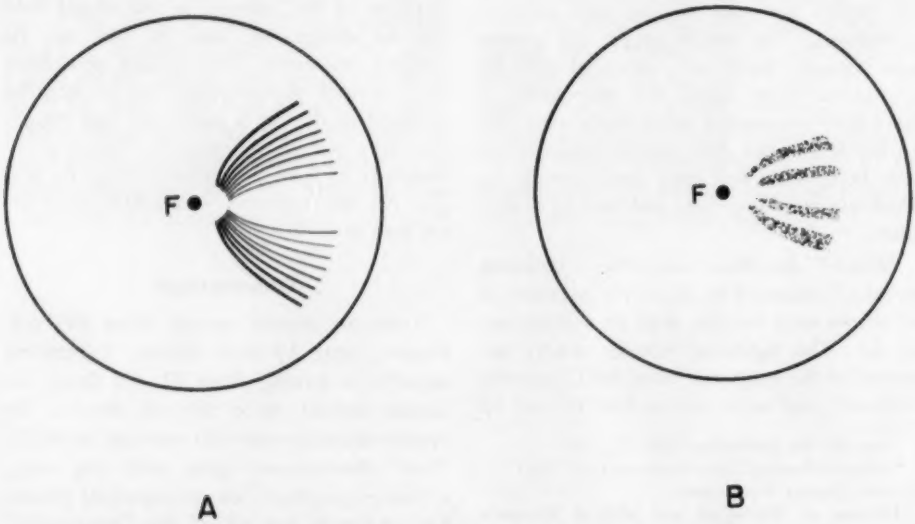

Fig. 1.—The phosphene of the right eye in a right-to-left flick. *A*, the phosphene pattern in the rested eye; *B*, the pattern after fatigue; *F*, fovea, as identified by the afterimage of a fixated inducing light.

are brillantly bright when first seen; as they are elicited repeatedly the whitish color shifts to an unsaturated purple or orange with greatly decreased brightness.

The size of the sheaf figure measured on a perimeter screen is about 20-40 degrees horizontally and vertically. According to Traquair,[11] this corresponds to 40-80 cm. on a screen at 1 meter. With fatigue the size of the phosphene dwindles to about 10 degrees in both directions.

The details of the sheaves are sharp, crisp, and clear in early observations and become indistinct and blurred as the phenomenon "fatigues." The best and largest figures are reminiscent of the projection of a hula skirt, and they show about 20 arcs. With fatigue the number dwindles to three or four. The apical region is not pointed but truncated; so it may be likened to the waist in the skirt simile (see Fig. 1).

If a sudden eye movement is other than horizontal, the only change of the phosphene is one of orientation and, possibly, size. The apex will point in any direction in which a flick is possible, but the size may diminish if the eye movement is less abrupt and forceful. Contraction predominantly involving the internal rectus always gives the largest and most detailed figure in any series of observations. The figure for each eye always remains in the temporal field with the apex about 10 to 20 degrees from the fovea, the separation varying with the direction in which the apex points. If the apex points away from the fovea, the central arcs of the sheaf may overlap the fovea or transgress it. Such a transgression is not marked by a change of intensity of the respective arcs. Vertical flicks require much practice but otherwise conform to the general scheme. The phosphenes lie temporal to the foveae with the apices near the horizontal line through the foveae, and with the bulk of the figures trailing in the "from" quadrants. In neither upward nor downward flicks were any differences seen between the phosphenes of the two eyes.

A complex experience was obtained upon rolling the eyes. This required practice and immediate recording in order to obtain consistent reproducible results. In this experience successive distinct phosphenes appeared in each eye. These may be likened to the tracks of an invisible cat circling an equally invisible tree.† In this simile the tree stands for the apparent center of gyration; the cat's tracks are successive phosphenes, each distinct from the next and apparently trailing closely the moving "gaze" of the closed eye.

Each eye sees an independent circle of cat tracks, the two circles having their respective centers in the temporal quadrants between 10 and 20 degrees from the fovea and near the horizontal meridian.

If the lighting is properly adjusted the whole series of observations can be carried out in a dimly lighted room facing a blackboard. The phosphenes can then be traced with a piece of chalk and measured with reference to the positions of the observer's eyes. In this open-eye procedure the phosphene is usually less prominent and less brilliant than with the closed eye. This type of experiment is subject to misinterpretation: The position of the horizontal flick phosphene may now seem to be in the general direction of the final gaze. Careful analysis, however, shows that as the eyes are rapidly moved from midposition to, e. g., the far left, the phosphene of the right eye still appears to the right of the center of the new gaze. The phosphene remains, then, in the temporal quadrant.

It thus appears that the apex of the flick phosphene is centered upon the optic disc. Thus it invariably appears in the temporal visual field. The horizontal extent of my own blind spot is 3 degrees on the horizontal axis from +15 to +18 degrees for the right eye and −15 to −18 degrees for the left eye, respectively. Measuring the horizontal flick phosphene in case of a right-to-left movement (Fig. 2), I find that the phosphene extends from about +10 to about +50 degrees in the right, or trail-

† Note, however, that the cat is walking backward; that is, its pawprints face in the wrong direction.

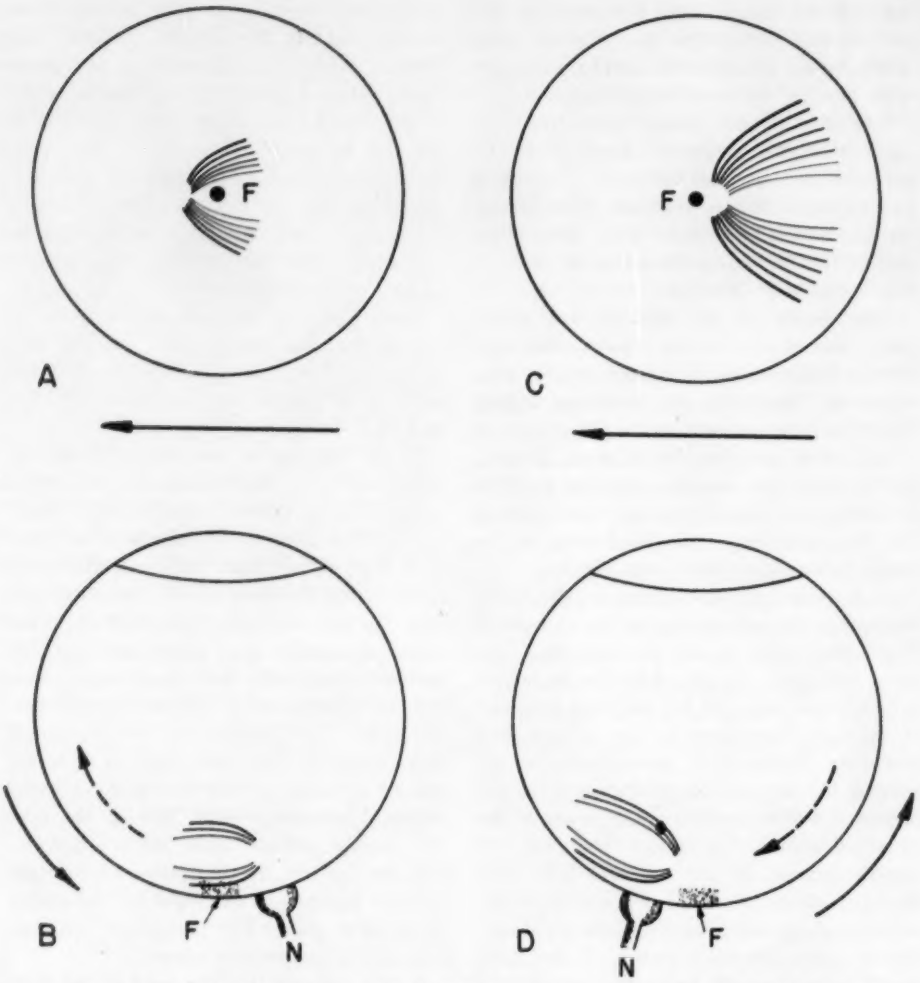

Fig. 2.—The phosphenes of a right-to-left flick and an interpretation relating to the topography of their origin. The upper two drawings show the phosphenes as seen. The lower two represent my projection of the phosphene back to the retina. The opposing arrows illustrate the shearing forces set up by the acceleration of the globe wall and the inertial retardation of the vitreous. *N*, nerve; *F*, fovea. The projected "phosphene" has been tilted and slightly displaced by artists license, to make it visible in the drawing.

ing, eye. Here the apex points nasad. In the left, or leading, eye the phosphene extends from about −20 degrees at the apex to 0 or +5 degrees distally—if the fovea is transgressed. For this eye the phosphene points temporad (Fig. 2*A* and *C*).

The flick phosphene is of only a moment's duration, appearing suddenly and then immediately and rapidly fading. The whole phenomenon is estimated to last about one-third of a second.

The sensation of the phosphene is simultaneous with the onset of muscle action. As my lids feel the motion of the eye, the phosphene has been or is being consciously recorded. If one accepts this at face value, it is implied that the phosphene is linked

with stresses set up at the onset of the flick, during the acceleration of the globe, not with the overshoot of the vitreous which supposedly occurs at the time of deceleration. This, then, allows one to draw a simple diagram of the shearing forces in each eye during the accelerative, or early, phase of the flick, including in the diagram the phosphene not as it is seen but (by simple geometry) its projected and assumed origin in the retina (Fig. 2*B* and *D*).

In the upper half of Figure 2 the phosphene is shown for each eye, together with a marker for the fovea. At *A* the phosphene of the left eye is seen pointing temporad, and smaller and paler than the corresponding phosphene in the right eye, shown at *C*. In *A* the apex of the phosphene appears farther from the fovea than at *C*. The distances drawn represent the best obtainable estimates. In *B* and *D* of Figure 2 the eyeballs are shown in horizontal section. The fovea *F* and the nerve *N* are indicated schematically. The projected and thus assumed site of the phosphene is superimposed, with a 45 degree tilt of the plane of the phosphene relative to that of the page. It thus seems that the missing apex of the sheaf figure represents the area of the disc. The bows of the phosphene may be likened to the streaming family of waves in the lateral wake of a ship in slow motion. Thus it would be acceptable to say that during a quick eye movement the region of the nerve head causes the phosphene through interaction with adjacent structures. However, the phosphene does not originate in the nerve head proper. The stress between the attachment ring of the vitreous and the mass of the vitreous proper is mechanically transmitted to the retina, causing elements to fire in the pattern of the phosphene seen. The posterior attachment ring of the vitreous, surrounding the nerve head, is believed to be the histological site corresponding to the apex of the phosphene.

The assumed deformation of the posterior face of the vitreous can best be visualized in a model experiment. A thin polyvinyl formal (Formvar) membrane is floated on water. A small wire loop is placed in the center of the surface of the membrane. If the loop is given a slight horizontal push, a set of folds appear in the "wake" of the loop which bear a remarkable resemblance to the shape of the flick phosphene sheaf. The relative lengths of the individual arcs are not strictly comparable to those observed for the flick posphenes. In the eye the bows are almost identical in length, while on the flat water surface the central rays are the longest. This difference is ascribed to the spherical curvature of the outer surface of the vitreous.

Other Observers.—There are six other observers, two local and four in other cities, who are able to see the flick phosphenes without difficulty. They describe figures essentially similar to my own in shape and behavior. Observer A remarks that her phosphenes exhibit a sharp apex, without blunting. Her drawings show straight rays, not arcs, with the whole sheaf located in the temporal quadrant. No explanation for the difference in observer A's observation is at hand. Observer D describes a certain degree of variability of the shape of the phosphene. I myself find a consistent difference in the phosphene of the left eye in case of a vertical upward flick. In this case and here only the blunt apex appears bridged and the distal, or tail, end of the sheaf carries a weakly luminous crescent. The outer margin of the crescent and the outermost rays constitute the periphery of a perfect circle. This gives my exceptional phosphene the closest approach I can obtain to the "fiery ring" of Purkinje [9,10] and the figure of Helmholtz.[5]

Observer B agrees completely with the general description of my own observations. He states that observing the phosphenes gives him a headache. Purkinje states that he also suffered from cephalalgia as a result of the exercise necessary to see his "fiery rings." Observer C places the phosphene in the "to" quadrant, with eyes open.‡

‡ It was Observer C who, having become interested in his own flick phosphene, inspired the present study.

This divergent report is ascribed to a misapprehension under which I myself labored until the marking of the fovea with an afterimage was suggested (Observer C was reporting on open-eye observations). At the end of a flick it is tempting to call whatever one sees in the training eye nasal, although it actually is temporal to the fovea.

Observer D states that he has been keenly aware of this and other phosphenes for the past 23 years. He gives credit to his teacher, W. D. Zoethout, for having had full cognizance of the flick phosphene and as having made it an optional class exercise. Perhaps due to this early and persistent training, Observer D states that in his experience the phosphene does not fatigue even with 180 consecutive flicks. He sees the same configuration as I, but he states that one eye gives much better results than the other. Observer D can observe his phosphenes during 24 hours of the day if the room is darkened (I can not). Observer E takes no exception to my general description. Observer F, after reading the manuscript, stated that he had observed the flick phosphene for not more than four years. He is now 51.

Age of Observers.—While the seven fully positive Observers A to F and I are now over 40, Observer D has seen the flick phosphene since his 20's. This is considered exceptional.

Health of Observers.—To the best of my knowledge, all fully positive observers are in good health. They have not reported any diseases of their eyes. (For my own examination, see Addendum.)

Negative or Partially Negative Observers.

As mentioned above, 39 research physicians and biologists answered a written questionnaire which was given to them after a brief explanation. Of the 39, there were 19 whose reports were totally negative. Thirteen saw rings, vertical streaks, or crescents; one observer reported seeing rings some of the time and at other times a large peripheral crescent, possibly related to the ora serrata. Of these thirteen, five localized the phosphene in the "to" quadrant, three thought it to be in the "from" quadrant, and five did not or could not determine its quadrant.

Distribution of Observers.—Of 39 persons who answered a written questionnaire (I am including Observer C and myself in this group), 19, or about 50%, are completely negative. Thirteen, or about 33%, see some form of the flick phosphene other than my own. Seven, or about 18%, are fully positive. (This group is overweighted by Observer C and myself). It seems, then, that 50% of this selected population with clinically normal eyes has some entoptic response from flick movements of the dark-adapted eye with closed eyelids in dark surroundings. While the 13 persons reporting some other flick phosphene are scattered over the entire age range, this is not true of the full-positives. It is my guess that if the inquiry were carried further but limited to persons over 40-45 and trained in biology and/or medicine at least 20% of full-positives might be found. Thus, in persons trained in self-observation and over 40-45 the flick phosphene is believed to be fairly common.

Comment

There is considerable evidence that the phosphenes of quick eye movement result from a primary deformation occurring at or near the posterior face of the vitreous. Hilding [6] has studied the mechanics and hydromechanics of the vitreous during such movements and finds that in acceleration and deceleration the vitreous lags behind the globe wall. He finds also that torsional (or shearing) forces at the interface of vitreous and retina are greatest when the outer layers of the globe wall attain their greatest velocity during the flick, and the inertial drag of the vitreous upon the retina is greatest at this time. The torsional forces of the surface of the vitreous are transmitted through the attachments of the vitreous to its immediate surroundings. Among beef eyes, Hilding [6] even found individual variations in the "slack and lag," hence in the

shearing forces in the "wake" of the loop forming the attachment.

Pischel [8] describes a slit-lamp appearance in patients with detachment of the vitreous thus: "The posterior face can be seen to undulate like a jellyfish in water due to the movements of the eye . . . when the vitreous shrinks it gradually pulls free from the disc," and then the vitreous almost always shows some form of annular opacity in its posterior membrane. A good description of the posterior face of the vitreous is also given by Wolff.[13]

My thesis may be stated as follows: Flick phosphenes originate as deformations of the posterior face of the vitreous. This deformation is transmitted directly to the retina and entoptically seen as the result of mechanical firing of unidentified elements. The elicitability of the phosphene represents a normal sort of vitreous "detachment" or looseness which occurs beyond a certain point in the life cycle. This "physiological" detachment as a precocious senescent phenomenon has "lots of company" in other parts of the eyeball.

Four of the fully positive observers I have located report stability of their observations over several years and to date. Others have only recently become conscious of the phenomenon. It would seem, then, that in all these observers the vitreous is still attached to the disc, but as a whole it can be assumed to have shrunk just enough to admit a very thin layer of subvitreal fluid. This layer I assume to be only a few micra thick. The subvitreous fluid layer would permit a patterned local deformation of the posterior face of the vitreous to occur and to impress itself mechanically upon the retina. If the shrinkage of the vitreous should progress (physiologically? pathologically?) without detachment around the disc, one might expect that the multiple-arc pattern would become faint and/or blurred, then both, then unobtainable. The normal flick phosphene of the present paper would then be replaced by that species of Moore's lightning streaks which is caused by more extensive vitreous detachment, as pointed out by Verhoeff in the discussion of Pischel's paper.[8] Future observations should show whether or not the clinical genesis of the full-blown detachment of the vitreous is sometimes or always preceded by a preclinical stage of varying duration during which the normal sheaf of arcs is seen.

The present phenomenon has nothing to do with Haidinger's brushes, the blue arcs of Purkinje, or any other sheaf-like entoptic appearance. It is related rather to other instantaneous entoptic effects of sudden local pressure upon the retina such as the ring of "light" one readily generates with a finger-tip at the outer canthus. It localizes the disc in the subjective visual field and to this extent is related to some other entoptic phenomena, especially Purkinje's fiery rings and Friedman's [4] observations.

Alternative explanations of the flick phosphenes may be considered. Direct deformation in the neighborhood of muscle insertions must be dismissed on several grounds. The angular measurements do not fit the topography of these insertions. The shape of the flick phosphene does not correspond to the aponeuroses of an extraocular muscle. It can be elicited in diagonal movements which bisect the angle between recti. Most important of all, its orientation in a given eye is reversed without change of its shape or the position of the apex, simply by reversing the direction of the eye movement. The possibility of an action-current spill from the innervation of the muscle to the retina must be dismissed a priori because of the wide separation of muscles and retina and because no such leak phenomena are known to occur generally. Much the most plausible earlier suggestion is that the flick phosphene is caused by pull on the optic nerve. Purkinje [9] (p. 81) "deduced the light of the 'fiery ring' to originate from the sudden stress on the optic nerve" (my translation). If this is tentatively accepted, it still begs the question of how this stress has its effect in the retina at the locus where the phosphene is obviously generated. Friedman [4] has suggested that the retina itself is pulled into a set

of folds, of which the phosphene is an image. I do not wish to dismiss this suggestion at all lightly, but it fails to appeal to me on the grounds of the architectural fine structure of the retina.

The present phenomenon may be normal, a physiological aura of local intraocular senescence, or it may be preclinically pathological. Clinical diagnosis may conceivably be aided by awareness of, and eventual better understanding of, the phosphene patterns described here. It is at least possible that in the "subclinical population" several types, or at least grades, of flick phosphene may be found, perhaps connecting definitely pathological lightning flashes with the apparently normal phenomenon of the present investigation. Further anatomical studies may reveal individual morphological differences (possibly inherited) in the attachments of the vitreous body into the region of the optic disc. Such differences might be related to variations in the phosphenes reported by individual observers and to items in ophthalmological histories the import of which could not otherwise be appreciated.

Summary

Eye movement phosphenes of a hitherto incompletely recorded but probably common type are described. Seven persons out of about one hundred, now all over 40, reported consistent and repeatable observations. The flick phosphene is ascribed to an instantaneous and transient deformation of the posterior surface of the vitreous emanating in a particular "polarized" pattern from its attachment at the optic disc. This deformation is due to an inertial lag of the vitreous when the eye is suddenly "flicked." The deformation is postulated to be directly transmitted to the retina and to cause, in the deformed regions on the retina, previsual activity which is observed entoptically as the flick phosphene in the dark-adapted and rested eye. The phenomenon is considered to be possibly an early senescent sign of a normal, slight shrinkage of the vitreous. This prerequisite condition differs from frank vitreous detachment, although the flick phosphene may be related to Moore's "lightning streaks." As a subclinical phenomenon, the flick phosphene may have potential diagnostic and prognostic value.

Addendum

After completion of the manuscript, my eyes were examined by Dr. Frank W. Newell, at the University of Chicago clinics, and by Dr. Alson E. Braley, at the University of Iowa. The reports are as follows:

Ocular Examination—Bernard R. Nebel, M.D. (Dr. Newell).—Vision is corrected to 20/20 in each eye with R. −1.50 cyl, ax 150; L. −1.75, cyl, ax 175. Externally, blepharochalasis is present. The anterior eye and orbit is otherwise normal. Intraocular pressure is 17 mm. of mercury (Schiøtz), right and left. The lenses show anterior cortical opacities plus coronary opacities. These developmental anomalies are considered to be without significance.

Ophthalmoscopic examination indicates the media to be clear; the discs are normal, with very small scleral crescents bilaterally; the maculas are normal. A small posterior vitreous detachment is readily visible in the left eye between the disc and the macula. Temporally, the optically empty space between the retina and the posterior boundary of the detached vitreous is very narrow, and it appears unlikely that the detachment extends much beyond the macula region. In the right eye a very small vitreous detachment is present between the disc and the macula, the optically empty space being slightly wider above than below.

Diagnosis: Myopic astigmatism.

Ocular Examination (Dr. Braley).—Dr. Nebel was examined on March 31, 1957. A contact lens was placed in the left eye, and the fundus was examined with the slit-lamp microscope. The vitreous was detached superiorly and slightly temporally, and the superior face of the vitreous extended down almost to the vicinity of Cloquet's canal. Cloquet's canal could be followed back to near the disc. At the disc the vitreous was

slightly detached. There was a clear space between the posterior face of the vitreous and the anterior layers of the nerve head. Over the macula the detachment of the vitreous was most interesting. Beginning at the fovea and extending toward the disc and temporally from the macula, the vitreous was detached in a circular manner, as if it were pushed away from the retina. There was a clear space between the posterior thin face of the vitreous and the anterior surface of the nerve fiber layers of the retina. This was particularly pronounced at the fovea. The posterior face of the vitreous was thrown into folds which looked like the ripples on a pond. These ripples apparently began near the point where the fovea centralis originated and extended temporally. If the light were adjusted correctly these ripples seemed to cast a slight shadow onto the retina. The vitreous was detached nearly the thickness of the retina. The right eye was not examined as completely as was the left eye, but a similar detachment of the vitreous was present in this eye. A. E. Braley, M.D.

The manuscript has been critically read by Drs. H. A. Blair, L. E. Lipetz, F. W. Newell, and Gordon L. Walls, all of whom have given me aid in the form of constructive suggestions.

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REFERENCES

1. Adler, F. H.: Physiology of the Eye: Clinical Application, London, Henry Kimpton, 1953.

2. Berens, C.; Cholst, M.; Emmerich, R., and McGrath, H.: Moore's Lightning Streaks: A Discussion of Innocuousness, Tr. Am. Ophth. Soc. 52:35-63, 1954.

3. Duke-Elder, W. S.: Text Book of Ophthalmology, Vol. 1, St. Louis, The C. V. Mosby Company, 1938.

4. Friedman, B.: Observations on Entoptic Phenomena, Arch. Ophth. 28:285-312, 1942.

5. von Helmholtz, H.: Helmholtz' Treatise on Physiological Optics, translated from the third German edition, edited by J. P. C. Southall, Ithaca, N. Y., The Optical Society of America, 1924, Vol. 2.

6. Hilding, A. C.: Normal Vitreous, Its Attachments and Dynamics During Ocular Movement, A. M. A. Arch. Ophth. 52:497-514, 1954.

7. Moore, R. F.: Subjective Lightning Streaks, Brit. J. Ophth. 19:545-547, 1935.

8. Pischel, D. K.: Detachment of the Vitreous as Seen with Slit-Lamp Examination, Tr. Am. Ophth. Soc. 50:329-345, 1952.

9. Purkinje, J. E.: Beobachtungen und Versuche zur Physiologie der Sinne, Prague, J. G. Calve, 1823, Vol. 1.

10. Purkinje, J. E.: Neue Beitrage zur Physiologie der Sinne, Berlin, Rainer, 1825, Vol. 2.

11. Traquair, H. M.: Clinical Perimetry, St. Louis, The C. V. Mosby Company, 1943.

12. Verhoeff, F. H.: Are Moore's Lightning Streaks of Serious Portent? Am. J. Ophth. 41: 837-840, 1956.

13. Wolff, E.: The Anatomy of the Eye and Orbit, Philadelphia, The Blakiston Company, 1952.

The Multiple-Pattern Tachystoscopic Visual Field Screener in Glaucoma

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The development of the multiple-pattern tachystoscopic visual field screener by Harrington [1] has made a highly useful new tool available to all interested in the detection of and care of glaucoma. Its usefulness in industrial medicine and other fields is also being increasingly documented.[2]

Both the need for epidemiologic study of primary glaucoma and the infinitely greater effectiveness of therapy undertaken early in the course of the disease make a reasonably accurate screening procedure for glaucoma a highly desirable goal, and some form of visual field testing can scarcely fail to be included in such a procedure. Since the time-consuming nature of classic methods of central field testing, plus the need for skilled operators to perform the test, almost precludes their use in mass screening techniques, the multiple-pattern tachystoscopic visual field screener has appeared to offer the best substitute yet found which can fill the needs for a reasonably accurate detection or exclusion of early defects in a short time, with easy performance of the test by nonphysician office help.

In an attempt to evaluate its usefulness in glaucoma case-finding, the multiple-pattern tachystoscopic visual field screener has been used routinely on all office patients 35 years and over, plus any younger persons in whom glaucoma was suspected, as a part of our procedures in this clinic. This report is an analysis of the first 1500 such examinations and the correlation between findings with the screener and with more classic methods of central field testing. Included in these 1500 examinations are tests on 67 previously known early glaucoma cases, some of open- and of some closed-angle type, some with definite visual field loss on ordinary field testing and some without, plus an additional 33 cases regarded as glaucoma suspects because of certain features of their objective examination or history. Otherwise, these 1500 examinations include only unselected routine office visits.

In this series of 1500 tests, 133 positive tests were found. Table 1 shows the distribution of these positive tests between previously known cases of glaucoma, new cases of glaucoma with positive findings explained by other obvious ocular or central nervous system pathology, and cases with findings regarded as false or resulting from pathology not immediately obvious. The "new glaucoma" group includes patients not previously known to have glaucoma but proved to have glaucoma by complete work-up subsequent to the initial screening.

In Table 2 the visual field findings as determined by the tachystoscopic screener and on the tangent screen in the 67 previously known glaucoma cases and in the 40 new glaucoma cases found during these tests are compared. The 67 known cases of

TABLE 1.—*Distribution of Positive Tachystoscopic Tests*

Condition	Cases with Positive Multiple-Pattern Fields, No.
Known glaucoma	39
New glaucoma	31
Other ocular or C.N.S. pathology	23
Pathology undetermined or false positives	40
Total	133

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From The Department of Ophthalmology, Bowman Gray School of Medicine of Wake Forest College and North Carolina Baptist Hospital.

This study was performed as part of a glaucoma study backed by a grant from the National Institutes of Health.

TABLE 2.—*Proved Glaucoma*

Field Findings	Known Glaucoma	New Glaucoma	Correlation *	
			Positive	Negative
Tachystoscopic positive, tangent screen positive	34	27		
Tachystoscopic positive, tangent screen negative	5	4	83	16
Tachystoscopic negative, tangent screen positive	9	1	Equivocal	
Tachystoscopic negative, tangent screen negative	19	8		
Total cases	67	40	107	

* Correspondence of findings on tangent screen and with multiple-pattern tachystoscopic screener in proved early glaucoma.

glaucoma were selected more or less at random from among our series of proved early glaucoma cases as a means of evaluating the degree of correspondence between field findings determined with standard techniques and with the tachystoscopic methods. These include cases of early simple glaucoma, some with and some without demonstrable field loss but all with consistently abnormal aqueous outflow and water provocative tests and, in addition, cases of closed-angle glaucoma which have either had congestive episodes or positive pupillary dilatation provocative tests. The eight cases listed as equivocal under the correlation column gave unreliable results on either the tangent screen or the tachystoscopic screener, or both.

Table 3 gives the results in 33 cases which were suspected of having early, or low-tension, glaucoma, along with the correlation between the standard and tachystoscopic testing methods. It is interesting and significant that in these equivocal cases the correlation between the methods is poorest.

TABLE 3.—*Results in Thirty-Three Glaucoma Suspects*

Positive Tachystoscopic Fields	Negative Tachystoscopic Fields	Correlation with Tangent Screen	
		Positive	Negative
8	25	21	12

Comment

The results of these tests indicate that the multiple-pattern tachystoscopic method for visual field testing is not only a quick but also a sensitive and accurate tool in glaucoma work, especially in glaucoma case-finding. Even in very early glaucoma, where the field changes are slight or absent, and often changing, the tachystoscopic method appears to be nearly as sensitive as standard central field techniques using the 1/1000 white isopter, and correspondence between the methods is somewhere between 80% and 90%, as judged from this relatively small series. It is only in the equivocal cases, which are often equivocal because of poor patient reliability, that the correspondence between the techniques becomes less.

Summary

The results of 1500 multiple-pattern tachystoscopic visual field screening tests are tabulated.

The findings in 67 previously known early glaucoma cases, in 40 new glaucoma cases, and in 33 glaucoma suspects are compared with central field findings as determined on the tangent screen.

The multiple-pattern tachystoscopic visual field testing method can be regarded as a reliable and useful aid in glaucoma case-finding and in glaucoma follow-up where standard techniques are not feasible or seem unreliable.

Bowman Gray School of Medicine, Wake Forest College (7).

REFERENCES

1. Harrington, D. O., and Flocks, M.: Multiple Pattern Method of Visual Field Examination, J. A. M. A. 157:645-651 (Feb. 19) 1955.

2. Robertson, L. T.: Use of the Harrington Multiple-Pattern Screener in Industry, Tr. Am. Acad. Ophth. 60:806-811 (Nov.-Dec.) 1956.

Innervation of the Corneal Endothelium of the Eye of the Rabbit

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The cornea is known to be supplied by a complicated system of nonmedullated nerve fibers which originate in the ciliary plexus. These nerves enter the cornea from the limbus in the middle layers of the stroma. They lose their myelin sheaths soon after entering the stroma and divide into many branches as they run centrally and anteriorly toward Bowman's membrane, which they penetrate through the pores. The nerve fibrils form a plexus beneath the epithelium, send up branches between the epithelial cells, and end in round or pear-shaped end-bulbs (Friedenwald[1]). Histologic evidence for the existence of three different types of nerve fibers in the corneal stroma has been described elsewhere (Wolter[2]). Surprisingly, however, the nervous system of the cornea is generally believed to be limited to the stroma, the subepithelium, and the epithelium. In the literature we find no histological reports indicating the existence of nerves and nerve endings in the corneal endothelium.

The corneal endothelium represents a single layer of flat, mesodermal cells at the posterior surface of the cornea. This layer has undoubtedly important functions. It is known to be responsible for the normal state of dehydration of the corneal stroma. Destruction or degeneration of the endothelium results in swelling, loss of transparency, and final scarification of stroma and epithelium of the cornea.

The question of whether there are nerves in the endothelial layer of the cornea or not is not discussed in most textbooks and papers on the subject (Parsons,[3] Lauber,[4] Duke-Elder,[5] Wolff,[6] Friedenwald,[1] Adler,[7] Thomas,[8] Dogiel,[9] Egorow,[10] Abraham,[11] Zander and Weddell,[12] Engelbrecht,[13] Vrabec,[14] and others). There are authors, however, who have expressed the opinion that the corneal endothelium does not contain any nerve fibers (Attias[15]; Agababow[16]).

This paper represents the description and photomicrographic recording of nerves in the corneal endothelium of the normal eye of a rabbit as evidence for the existence of such nerves.

Material and Method

Normal eyes of rabbits were fixed in bromformalin (solution of Cajal). The corneae were isolated by a cut through the limbal area with a razor blade. Flat sections of the corneae were made on the freezing microtome. The panoptic silver carbonate method of del Rio Hortega was used to stain these sections. The technique and the possibilities of this method are described in detail by Scharenberg and Zeman.[17] All illustrations contained herein are unretouched photomicrographs.

Histological Description

Fragments of nerve fibers were seen in the corneal endothelium of several normal rabbit eyes. In the endothelium of one normal rabbit cornea, however, it was possible to stain the whole course of one nerve fiber continuously from the limbus area

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Fig. 1.—Main nerve on its course in the peripheral endothelium of the rabbit, with dichotomic division into branches. See Section *1* of Figure 7. Hortega method; photomicrograph.

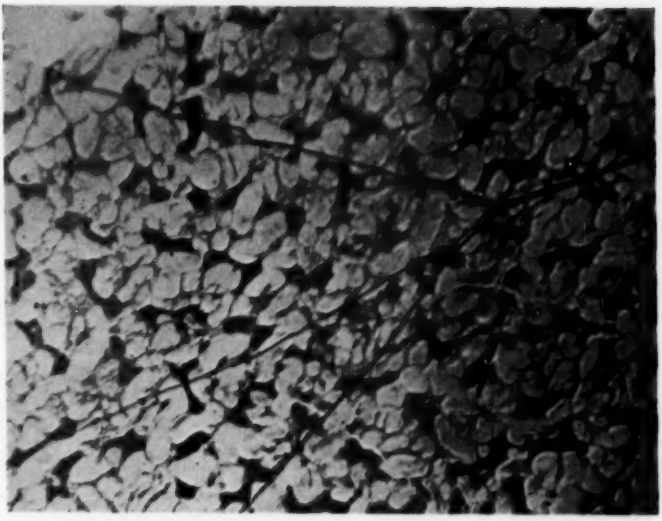

Fig. 2.—Further dichotomic branching of the nerve fiber in the endothelium of the rabbit. The nerve fibers have close relationships to the protoplasm of endothelial cells. See Section *2* of Figure 7. Hortega method; photomicrograph.

toward the center. This nerve, its branches, and its terminations will be described here. A reconstruction of the nerve fiber with its main branches is presented in Figure 7.

Our sections do not allow for a discussion of the origin of this endothelial nerve fiber. The main fiber is already seen in the endothelium in the extreme periphery of our sections. It runs right through the middle of this single layer of flat star-shaped cells, in very close contact with the protoplasm of these cells. No cells of Schwann are seen accompanying the nerve. The main fiber branches dichotomically (Fig. 1). Both of its branches divide again and again after irregular distances (Figs. 2, 3, and 4) and supply a sector-like area of the endothelium with nerves. The fibers become very delicate after repeated branching (Figs. 5 and 6). Clearly, they run partly within the protoplasm of endothelial cells and sometimes have close relationships to the cellular nuclei. The terminal fibers are still clearly visible in the sections, but they are so fine

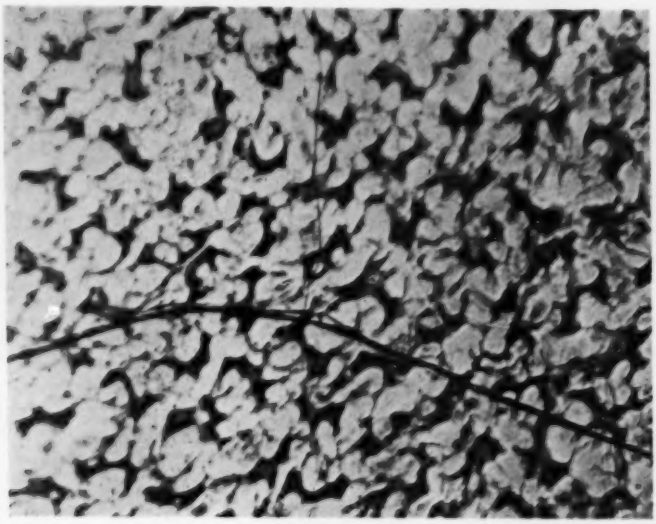

Fig. 3. — Two small nerve fibers leave a main branch of the rabbit endothelium at almost right angles. See Section *3* of Figure 7. Hortega method; photomicrograph.

Fig. 4. — Dichotomic branching of finer nerves at the margin of the slide of the corneal endothelium. See Section *4* of Figure 7. Hortega method; photomicrograph.

Fig. 5.—Two nerve fibers of different sizes in the corneal endothelium of the rabbit. The hook formation of the thicker nerve fiber at its lower end in the picture is an artefact. See Section *5* of Figure 7. Hortega method; photomicrograph.

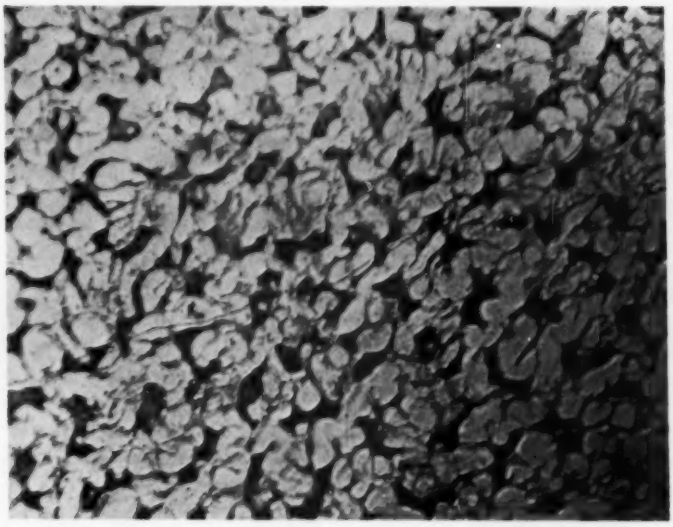

Fig. 6.—This fine nerve fiber of the corneal endothelium of the rabbit runs through the protoplasm of the endothelial cells and often has close contact with the cellular nuclei. This is not a terminal fiber, but it is about the finest nerve to be recognized in a photomicrograph. See Section 6 in Figure 7. Hortega method; photomicrograph.

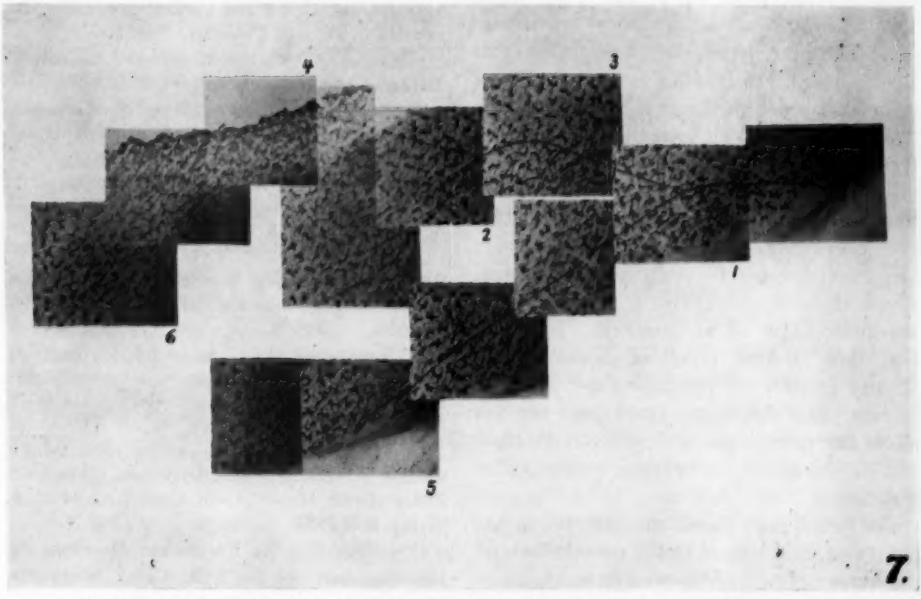

Fig. 7.—Reproduction of a photomicrographic reconstruction of a branching nerve fiber which supplies a sector-like area of the endothelium of a normal rabbit eye. Figures 1 to 6 represent sections of this reconstruction at high-power magnification.

that it is not possible to see them in photomicrographs.

It is my impression that the terminal branches of the described nerve fibers end with very delicate, network-like structures which extend into the protoplasm of endothelial cells. Only a few of all endothelial cells, however, are seen to be supplied by such nerve endings.

Nerves of the type described here are the only nerve structures found in these sections of the rabbit endothelium. No other

endings or end-apparatus are seen besides these fine network-like terminations. The endothelial cells which are supplied by the nerve endings do not look in any way different from those without such endings.

Comment

The present findings are evidence for the existence of nerve fibers in the normal corneal endothelium of the rabbit eye. These nerves run and branch within the endothelial layer. They have a close relationship to the endothelial cells but possess no accompanying cells of Schwann or similar elements. Their endings represent extremely delicate network-like structures which extend into the protoplasm of endothelial cells. A special technique of corneal sectioning would be necessary to visualize the origin of these nerves. Obviously, they enter the endothelium in the extreme periphery. It is possible that these nerves do not originate from the corneal nerve bundles in the stroma but somewhat more posterially.

The course and the type of branching and termination of the endothelial nerves is very similar to that of the second type of nerve fibers of the corneal stroma of the rabbit eye previously described.[18] These nerves also run through the cells of the stroma, divide dichotomically, and terminate within the protoplasm of stroma cells. I believe that this "second type" of fibers in the stroma is part of the automonic nervous system. My anatomical study does not yet allow any conclusions as to the classification and functions of the nerves in the endothelium.

So far, I have been unsuccessful in attempts to stain nerves in the endothelium of the human cornea. However, it seems likely that improved techniques may enable us someday to visualize such nerves also in man.

Summary

This paper is a description and photomicrographic recording of nerves in the corneal endothelium of the normal eye of a rabbit.

Neuropsychiatric Institute, University Hospital.

REFERENCES

1. Friedenwald, J. S. and others: Ophthalmic Pathology: An Atlas and Textbook, Philadelphia, W. B. Saunders Company, 1952, p. 16.

2. Wolter, J. R.: Über den Aufbau der Nervenbündel in der Hornhaut des Kaninchenauges, Klin. Monatsbl. Augenh. 129:20-26, 1956.

3. Parsons, J. H.: The Pathology of the Eye, New York, G. P. Putnam's Sons, 1904, p. 150.

4. Lauber, H.: Die Hornhaut, in Handbuch der mikroskopischen Anatomie des Menschen, edited by W. von Möllendorff, Vol. 3, Pt. 2, Berlin, Springer-Verlag, 1936.

5. Duke-Elder, S.: Text Book of Ophthalmology, Vol. 1, St. Louis, The C. V. Mosby Company, 1940.

6. Wolff, E.: The Anatomy of the Eye and Orbit, Philadelphia, The Blakiston Company, 1948, p. 37.

7. Adler, F. H.: Physiology of the Eye, St. Louis, The C. V. Mosby Company, 1953, p. 40.

8. Thomas, C. I.: The Cornea, Springfield, Ill., Charles C Thomas, Publisher, 1955, p. 37.

9. Dogiel, A. S.: Die Nerven der Cornea des Menschen, Anat. Anz. 5:483-494, 1890.

10. Egorow, I.: Nervenelemente der Cornea im Meerschweinchenauge, von Graefes Arch. Ophth. 131:531-553, 1934.

11. Abraham, A.: Microscopic Innervation of the Cornea with Reference to the Neural Connections of the Fibrocytes, Acta biol. acad. sc. hung. 4:31-76, 1955.

12. Zander, E., and Weddell, G.: Observations on the Innervation of the Cornea, J. Anat. 85:68-81, 1951.

13. Engelbrecht, W.: Die epithelialen und subepithelialen Nervenendigungen in der menschlichen Hornhaut, von Graefes Arch. Ophth. 154:65-78, 1953.

14. Vrabec, F.: Bemerkungen zur normalen und pathologischen Innervation der Cornea, Wissensch. Ztschr. Ernst Moritz Arndt Univ. Greifswald 4: 99-104, 1954-1955.

15. Attias, G.: Die Nerven der Hornhaut des Menschen, von Graefes Arch. Ophth. 83:207-316, 1912.

16. Agabow, A.: Über die Nerven in den Augenhäuten, von Graefes Arch. Ophth. 83:317-380, 1912.

17. Scharenberg, K., and Zeman, W.: Zur Leistungsfähigkeit und zur Technik der Hortegaschen Silberkarbonatmethoden, Arch. Psychiat. 188:430-439, 1952.

18. Wolter, J. R.: Über 2 verschiedene Nerventypen im Hornhautstroma des Kaninchenauges, Ztschr. Zellforsch. 41:521-531, 1955.

Evaluation of Scleral Tucking Procedure for Retinal Detachment

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Recently, Everett [1] described his operation producing an external scleral fold in the treatment of detachment of the retina. According to Everett, such scleral folding, or tucking, is deemed worthy of serious consideration because it is technically simple and should, theoretically, produce the same result as the more extensive and complicated scleral resection. We became curious to study the histologic changes in the sclera created in this procedure, with a view to evaluating, if possible, the effectiveness and permanency of the operation.

It was our intention to create an outward fold of sclera, pass sutures through the fold, and examine the tissues after suitable intervals of time in order to ascertain whether adhesions formed between the scleral surfaces brought into apposition in this simple manner. We wished to determine whether a solid union would result and whether fibrosis and scar formation would ensue in the fashion of a healing wound.

It is a well-authenticated fact that after scleral resection, or lamellar resection, even though the scleral wound is well approximated by thorough suturing, the globe gradually regains its original size. We wanted to know whether the same thing would happen after scleral tucking by Everett's method. For that reason this experiment was undertaken on rabbits' eyes.

We carried out the procedure of scleral folding on six eyes of white rabbits and planned to study two of the eyes 4 weeks postoperatively, two eyes 8 weeks postoperatively, and the final two eyes 12 weeks postoperatively. The procedure was carried out according to the technique of Everett.

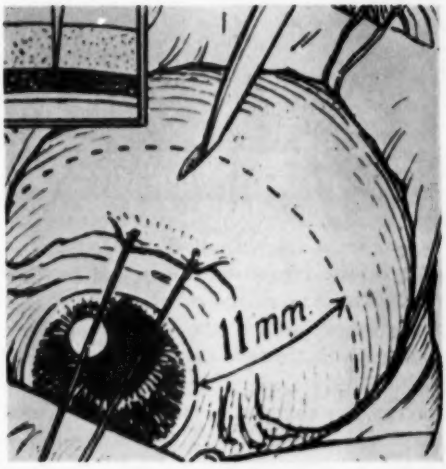

Figure 1

Figure 1. An incision was made in the conjunctiva over the superior portion of the eyeball, and the flap was reflected. The superior rectus muscle then came into view, and it was detached in order better to expose the scleral surface. Next, an incision was made through the sclera with a Bard-Parker knife. With Stevens scissors, one side of the scleral wound was very cautiously undermined, creating a cleavage plane between the sclera and the suprachoroid. Great care was taken to hug the inner surface of the sclera and avoid choroidal bleeding.

Figure 2. Next, the cyclodialysis spatula was passed into the suprachoroidal space and the area of sclera was freed from the underlying choroid. The maneuver was done

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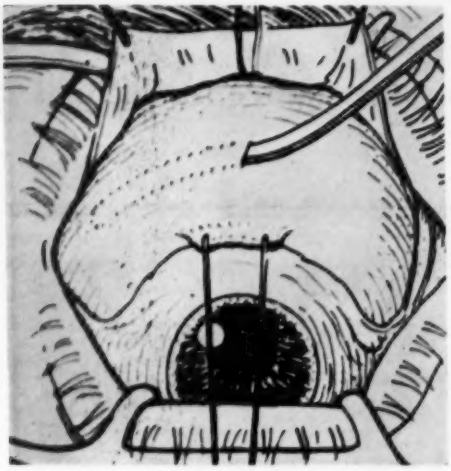

Figure 2

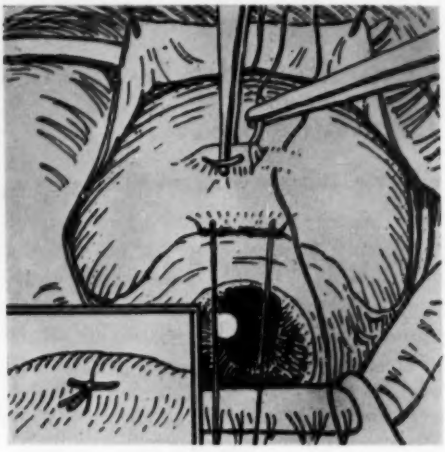

Figure 3

very carefully to avoid injury and penetration of the choroid and retina.

Figure 3. When the sclera had been sufficiently mobilized, the assistant grasped the loosened area of sclera with fixation forceps, bunching it up into a true scleral fold. Through this fold, the surgeon then passed a heavy black nonabsorbable surgical (silk) double-armed suture, in mattress fashion.

Figure 4. A second double-armed suture was inserted about 5 mm. away from the first. The two mattress sutures were tied very tightly through the scleral fold.

Figure 5. The conjunctiva was then closed with two or three interrupted finer silk sutures.

Postoperatively, the rabbits were given 60,000 units of procaine penicillin daily for one week. The animals were well cared for and appeared entirely healthy otherwise. The rabbits' eyes were enucleated according to plan—two at 4 weeks, two at 8 weeks, and two at 12 weeks. The eyes were fixed in Bouin's solution and embedded in paraffin, and sections were prepared for histologic study.

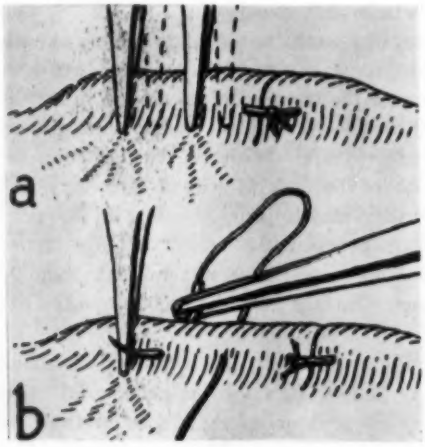

Figure 4

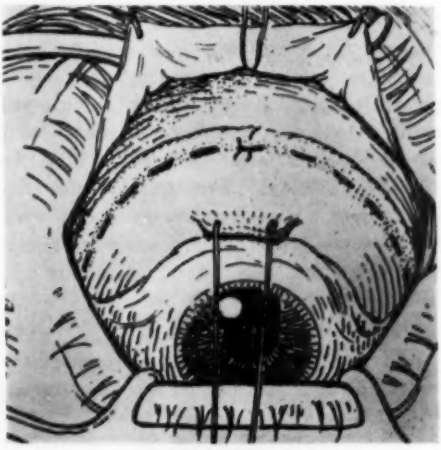

Figure 5

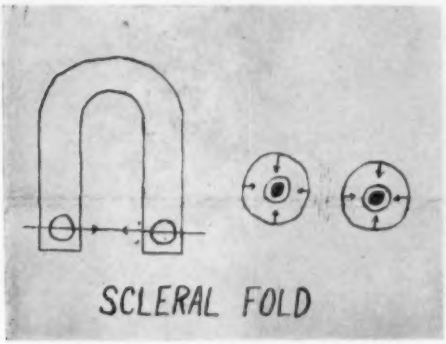

Figure 6

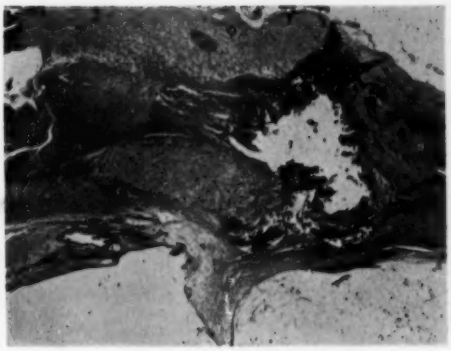

Figure 7

In order better to orient ourselves on the histologic sections to follow, we prepared a schematic diagram of a scleral fold (Fig. 6). Here we see a very simplified drawing of the two limbs of the scleral fold. At the base of each limb is a hole representing the track of the suture. Between the two limbs is an empty space where new granulation tissue must form if solid union is to result. An ideal section through the base of the scleral fold passes directly through the suture track on both sides. Projected in cross section, the two limbs of the scleral fold appear more or less circular, with a smaller circular hole within, representing the track of the suture. Within the suture track can be seen the actual fibers of silk constituting the suture material.

There are two elements which we must consider seriously in evaluating the results of the operation. The first is the closure of the suture track, which would be represented histologically by gradual disappearance of the central hole. The second element to be considered is approximation, or coaptation, of the two limbs of the scleral fold, which would be represented histologically by obliteration of the central empty space. The histologic sections to follow should be viewed in the light of this schematic cross section.

Figure 7 is a section through the scleral fold of an eye enucleated after four weeks. There is no evidence of closure of the suture track.

Figure 8 is another section of a four-week eye, showing some indication of beginning healing.

Figure 9 is a higher magnification of the same eye, showing fresh granulation tissue forming in a few areas, with early fibrosis.

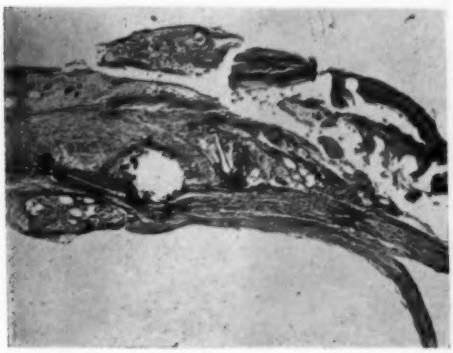

Figure 8

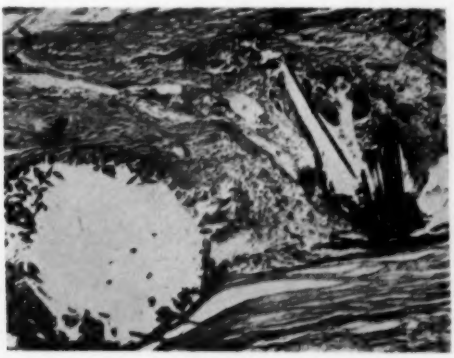

Figure 9

Figure 10

Figure 11

Figure 10 is a section through the scleral fold of an eye enucleated after eight weeks. There is some very early healing and fibrosis, with a few new capillaries visible. The suture track, however, is still largely open.

Figure 11 is another eight-week eye, showing a foreign body reaction. There is no evidence of union, coaptation, or healing.

Figure 12 is another section of an eight-week eye, in which one hole is almost closed and one still open.

Figure 13. The same section, under higher magnification, shows a foreign body reaction, with some indication as well of young fibrous tissue.

Figure 14 is a section through a 12-week eye, showing some union. One hole is still not filled in. There is practically no difference from the previous eight-week section.

Figure 15 is another section of a 12-week eye.

Figure 16. Under higher magnification, one can see almost complete filling in of the space between the two limbs of the scleral fold with newly formed tissue, following fragmentation of the suture. This would probably be a help in strengthening the coaptation of the fold. The section shows more definite fibrosis and firmer adhesion than any of the others.

After 12 weeks, then, there is just beginning to be evidence of solid union. It is possible, of course, that, in future weeks, the adhesions may become firmer. However, the scleral tuck stays in place for at least 12 weeks and most likely for a much longer period than that. This is more than sufficient time to allow for firm adhesions between choroid and retina as a result of the diathermy reaction. It would appear from this

Figure 12

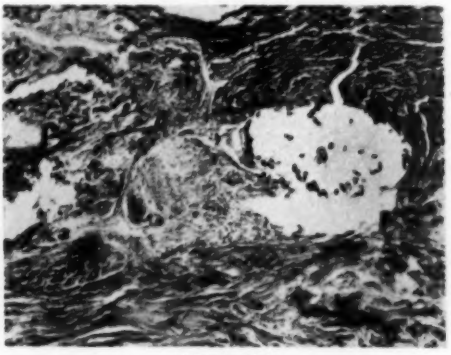

Figure 13

Figure 14

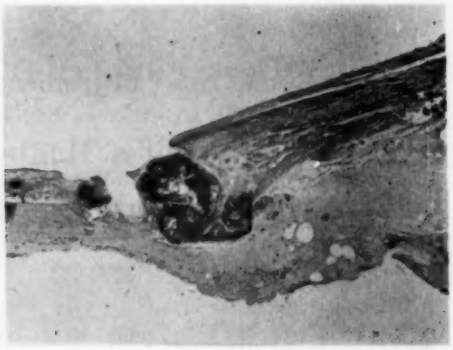

Figure 15

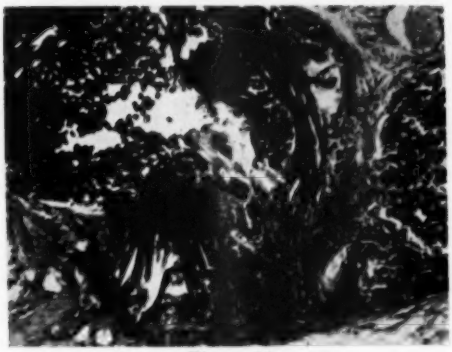

Figure 16

study that scleral tucking has great merit in detachment surgery.

The specimens were prepared by Miss Richardson, and Dr. David Wexler helped with the microscopic studies and evaluations.

8 E. 84 St. (28).

REFERENCE

1. Everett, W. G.: A New Scleral Shortening Operation: Preliminary Report, A. M. A. Arch. Ophth. 53:865-869 (June) 1955.

A Combination of a Magnetic Tangent Screen with the Harrington Multiple-Pattern Field Screener

GEORGE S. ZUGSMITH, M.D., San Pedro, Calif.

At the 1953 Session of the American Academy of Ophthalmology and Otolaryngology Conover and Spaeth [1] described an instrument which was devised to obtain more accuracy in central field examinations in less time than was usually required for this examination with other tangent screens. A concealed magnet was used to move the test object. The magnet moves through an open calibrated channel.

Harrington and Flocks [2] described the multiple-pattern visual field screener in 1954. They describe it as being an instrument for rapid qualitative examination which uses patterns printed in white fluorescent sulfide ink on 14 by 18 in. white cards; the fixation point is a 5 mm. black dot.

In an article summarizing recent instruments for perimetry, I [3] suggested the possibility of combining the two instruments to eliminate a piece of apparatus in the office.

The Harrington-Flocks screener was prepared by having a nonferrous top made which was covered with flocking.* The back, or outside, surface had painted on it tangent screen circles accurate for 330 mm., and a fixation point was placed on the inside. Magnetic test objects identical to those used on the Conover-Spaeth campimeter, were procured,† and the results were found to be comparable to those of Conover and Spaeth. There are two other advantages beside the one mentioned previously. 1. A fluorescent test object cemented to the head of a thumb tack can be used, with the known advantages possessed by fluorescent test objects. 2. The modification of the Harrington and Flocks screener is less expensive than the purchase of another instrument.

529 W. 8th St.

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* Jenkell Davidson Co., San Francisco.

† Geo. P. Pilling & Sons Co., Philadelphia.

REFERENCES

1. Conover, W. G., and Spaeth, E. B.: Conover-Spaeth Magnetic Campimeter, Tr. Am. Acad. Ophth. 59:542 (July) 1955.

2. Harrington, D. O., and Flocks, M.: Visual Field Examination by a New Tachystoscopic Multiple-Pattern Method, Am. J. Ophth. 37:719 (May) 1954.

3. Zugsmith, G. S.: Present-Day Perimetry, Eye, Ear, Nose & Throat Month., to be published.

A New Method of Measuring Interpupillary Distance

MAX UNGER, M.D., New York

Physical optics is an exact science. When used for refraction of human eyes, however, it becomes an art, because it deals with two uncertain variables, the examiner and the person examined. It will reflect the reactions of each. No matter how careful and painstaking the examiner and how cooperative the patient, there are many patients who still complain of eye strain. This is due to the fact that some things must be estimated, according to the response of the patient and the judgment of the physician. Many of these unsatisfactory cases result from incorrect estimation of the interpupillary distances for far and near work. The methods of estimating the interpupillary distance (P. D.) are too well known to require much discussion. The most frequently used for distance is the method of squinting first with the right eye and then with the left over the edge of a ruler held in front of the patient's eyes. After the P. D. for distant vision is estimated, a deduction of 1, 2, or 3 mm. is made for near vision, which is pure guesswork. In spite of the greatest care, some of the patients afterward complain of eye strain.

I believe that the devices and method of using them that I will describe will help take the guesswork out of estimating the P. D. and will help give the patient a more comfortable result. The devices consist of two circular disks with a centrally placed tubule in each, as shown in Figure 1. The disks are of a suitable size to fit into a trial frame. To get the P. D. for distant vision, the disks are placed in the trial frame in front of the lenses that have been finally selected so that the opening of the tubule is in line with the optical center of the lens behind it, as shown in Figure 2. The patient looks at the distance chart, puts his fingers on the screw that moves the lenses in and out, and turns the screw till he sees the chart with each eye. If the lenses are too close together or too far apart, he will see

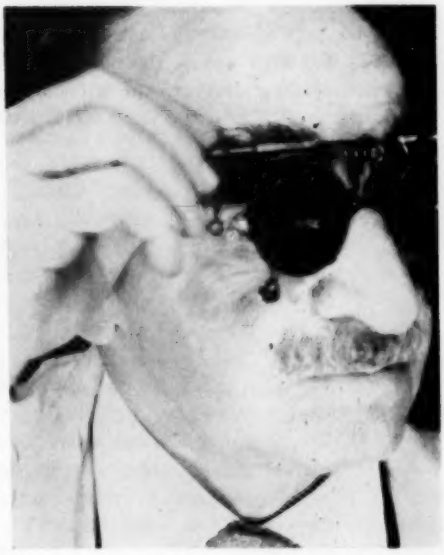

Fig. 2.—Patient manipulating disks.

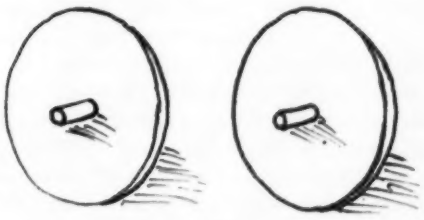

Fig. 1.—Disks with centrally placed tubules, for insertion in trial frame in front of lenses.

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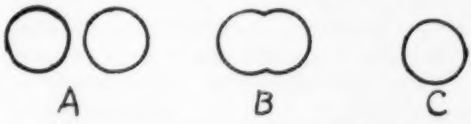

Fig. 3.—*A*, two openings seen when disks are too near or too far apart; *B*, openings beginning to fuse; *C*, one opening seen when disks are in correct position.

the chart through two separate holes, as shown in Figure 3*A*. He continues turning the screw till the two holes begin to fuse, as shown in Figure 3*B*. The patient keeps turning the screw until the two circles have fused into one (Fig. 3*C*). The P. D. for distant vision is then read off on the bar across the top of the trial frame. To get the P. D. for near vision, the patient holds a Snellen reading chart in one hand at the distance at which he expects to work with his near vision glasses and manipulates the lenses in and out as before. The distance between the indicators on the horizontal is read off again.

This method takes the guesswork out of estimating the pupillary distance for far and near vision. I have found that setting the lenses, especially the near lenses, at the proper distance relieves many cases of eyestrain that otherwise seem intractable.

36 W. 40th St.

Ophthalmological Reviews

Toxoplasmic Uveitis

J. V. CASSADY, M.D., South Bend., Ind.

There have been so many references to toxoplasmosis as it relates to ophthalmology, during the past few years, that it seems to be developing into an American epidemic. This has occurred largely since 1937, after Sabin and Olitsky (1935) rediscovered the organism during their study of neurotropic viruses.[1] Then, after Helenor Wilder,[2] in 1952, published her findings of Toxoplasma organisms in 41 eyes removed from patients between the ages of 16 and 72 years, a new interest about the importance of Toxoplasma in granulomatous uveitis was incited. Two schools of thought have developed about the role of toxoplasmosis in causing uveitis; one minimizes its significance and almost says it is unimportant, while the other group overemphasizes its moment and consequence in causing uveitis.

Toxoplasmosis is widespread in man and animals; its distribution in nature extends from the most primitive to the most highly developed. It is found in rodents, insectivora, carnivora, artiodactyla (swine, sheep, cattle), fox, monkey, chimpanzee, baboon, birds, and reptiles, but so far it has not been found in amphibia. The organism is crescentic, or arc-shaped, 2μ to 4μ in width and 4μ to 7μ in length. It is a fragile organism, easily destroyed by drying, freezing, heat, and disinfectants.

In animals, after the organisms have proliferated at the site of infection, a parasitemia develops. As antibodies appear the parasitemia clears, but organisms remain in the brain, in the adrenals, and in the heart after they have cleared from other organs. Proliferative forms of the organism invade cells, multiply, and burst the cell walls. Cysts that are found in the chronic stage persist in retinal tissue, lying dormant for years long after the acute infection has entered a chronic, quiescent stage. These cysts can rupture, releasing organisms and antigen to incite an allergic or a necrotizing reaction of the affected tissue cells. The persistence of Toxoplasma in the eye and in the brain may be caused by organism specificity for nerve cells or may be due to lack of diffusion of antibodies into the eye and into the brain. Rupture of pseudocysts, with a proliferation of parasites and a release of antigen into the tissues, may produce exacerbations of retinochoroiditis.

Toxoplasmosis usually occurs asymptomatically, or at least in an unrecognizable form. Siim[4] has described four types of acute disease which may be considered as the first stage:

(1) A typhus-like illness, with fever, chills, a red macular exanthum, cough, and, at times, meningoencephalitis

(2) A cerebrospinal form, with fever, delirium, convulsions, and lymphadenopathy

(3) A febrile lymphadenitis with glandular fever

(4) A nonfebrile subclinical lymphadenopathy with tender and enlarged lymph nodes but without other symptoms.

The four types have been described in laboratory workers.

The second stage may be considered as a subclinical period in which the organism becomes encysted and is harbored asymptomatically. The third stage is a clinical stage, in which, as ophthalmologists, we recognize manifestations of retinochoroiditic inflammatory activity.

Congenital toxoplasmosis, which is well known and has been extensively studied and recognized, consists of an encephalomyelitis

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with an associated retinochoroiditis in infancy. The cerebral manifestations may vary in intensity from microcephaly to hydrocephalus, and in these cases cerebral calcification often is demonstrable by roentgenograms. The ocular pathology, a granulomatous retinochoroiditis, unilateral or bilateral, can be minimal, or it may be extensive, associated with nystagmus and central or peripheral blindness.

Presumably, congenital toxoplasmosis only occurs in infants whose mothers acquire the infection during gestation, and so, fortunately, subsequent children show no evidence of the disease. Rats, however, with chronic infection have transmitted toxoplasmosis to their offspring. Sows with low dye test titers and asymptomatic infections have given birth to infected pigs. Feldman [5] says that the congenital disease results when a nonimmune pregnant woman happens to acquire an inapparent infection. The resultant parasitemia permits Toxoplasma organisms to set up a nidus in the placenta from which infection in the fetus follows. In 204 mothers studied by him, none had subsequent infected offspring. Most infants with toxoplasmosis have some residual damage, but they usually survive.

The third, or chronic, stage, the one that most concerns us as ophthalmologists, is not easily recognized. The organisms are encysted, and the cyst walls may be so tough as to prevent the escape of antigenic and chemotactic substance, so that (according to Frenkel [6]) the cysts do not cause any inflammatory reaction. It is not possible to determine by serologic or skin tests whether the person still harbors the infection. Except for serum antibodies against Toxoplasma and bouts of retinochoroiditis or granulomatous uveitis, we know little of this chronic stage.

Toxoplasmosis is important to ophthalmology because it seems to be one of the main causes of granulomatous uveitis. It can be estimated that Toxoplasma may be the agent that evokes 65% to 70% of cases of granulomatous uveitis with retinochoroiditis. Positive toxoplasmin skin tests and positive methylene blue dye tests are found in 10% to 15% of the young adult and 35% to 40% of the older age group of the general population. This widespread presence of antibodies to Toxoplasma in human serum means that unrecognized toxoplasmosis must frequently occur. Patients showing a positive skin or dye test may have granulomatous uveitis, and, in these patients, the uveitis may or may not be caused by Toxoplasma.

Antibodies to Toxoplasma as evidenced by a positive skin test or dye test have been reported at times in patients with Sarcocystis, Trichomonas, and Trypanosoma infections, but Cathie [7] disproved this, at least as regards Trichomonas infections, by comparing the dye test in women in the same age group with and without such infection. He concluded that a positive dye test in women with Trichomonas infection did not preclude the presence of both infections The only absolute proof of the presence of active toxoplasmosis is the isolation of the organisms. This isolation is usually not practical, and so we are compelled to make a presumptive diagnosis of toxoplasmosis.

When we suspect that toxoplasmosis is the cause of a patient's uveitis, it must be a granulomatous uveitis involving the posterior segment of the eye. The lesion is primarily in the retina, with the choroiditis, the vitreous opacities, the anterior uveitis, and the other ocular pathology secondary to the retinitis. The occasional retinal periphlebitis, optic neuritis, and retinal exudate with serous detachments are also secondary to, but occur at times with, the retinitis. Isolated iridocyclitis rarely occurs. Active retinochoroiditis lesions may be single or multiple in one or both eyes, but they are most characteristically seen directly adjacent to healed areas of previous inflammation.

Before it is assumed that the cause of granulomatous uveitis is toxoplasmosis, other possible causes of uveitis must be ruled out, by a thorough clinical and serological survey for evidence of other systemic diseases, such as diabetes, sarcoidosis, nephritis, leukemia,

tuberculosis, and respiratory, gastrointestinal, or urologic disorders. Serologic tests for brucellosis, tularemia, and syphilis; serum albumin-globulin ratio; antistreptolysin titers, and blood chemistry studies are often necessary for a complete survey. Roentgenograms of the chest, sinuses, skull, and, at times, of the gastrointestinal tract and the hands and feet may be needed. X-ray evidence may point to pulmonary lesions, cerebral calcification, sinus or gastrointestinal disease, or sarcoidosis. Intradermal old tuberculin, histoplasmin, and toxoplasmin skin tests are a part of the survey to find the cause of granulomatous uveitis. Blood serum tested by the methylene blue dye test for toxoplasmosis should also be included in this survey.

Before discussing the significance of the toxoplasmosis dye and skin test, I should like to list the requirements for making the diagnosis of toxoplasmic uveitis. In addition to the ruling out of other causes, the uveitis must be of a definite clinical pattern, as has been described, and the person must have antibodies against Toxoplasma. In addition, two other suggestive criteria for the presumptive diagnosis are, first, the failure of the uveitis to respond to antituberculous therapy and, second, the favorable response to specific antitoxoplasmic therapy. Perkins and Smith [8] gave one group of uveitis patients placebo tablets and a second group pyrimethamine tablets for a period of a month. A definite improvement was noted in the uveitis of those patients who had been treated with pyrimethamine as compared with those treated with placebos, provided that they had positive dye tests. In order to be effective, pyrimethamine should be given in large doses. When it is given in only a 25 mg. daily dose without the addition of synergistic sulfonamide, it is difficult to evaluate the significance of a lack of response.

To interpret the toxoplasmin skin and dye tests it is important to remember that posterior granulomatous uveitis occurs during the third, or chronic, stage of toxoplasmosis, long after the acute disease has subsided and after many of the antibodies have disappeared. The toxoplasmin skin test is performed by the intradermal injection of 0.1 cc. of toxoplasmin antigen in one forearm, with a similar control injection in the other arm. Eli Lilly and Company make the antigen from peritoneal exudate of Toxoplasma-infected mice. The toxoplasmin control is made from uninfected mouse spleen. The test is read within 48 hours, exactly like the intradermal test for tuberculosis. Frenkel [9] originally believed that the test should be considered positive if 10-30 mm. of induration and 10-50 mm. of erythema were present after 48 hours. In a recent personal communication, he now does not believe that such an extensive reaction is necessary, but that any appreciable difference between the reaction to the antigen as compared with the control is significant. The reaction may be marked within 24 or may be delayed for 72 hours. If the test is equivocal, it should be repeated. A positive toxoplasmin skin test does not mean that the patient has active toxoplasmosis, but indicates that he has antibodies against Toxoplasma as a result of previous toxoplasmic infection.

A negative reaction does not always rule out toxoplasmosis as a cause of the uveitis. At times the skin test is negative when the dye test titer is extremely high. This incongruity may be explained by an intense concentration of antibodies in the serum, so that the small amount of intradermal antigen incites no local reaction. The toxoplasmin skin test has a close correlation with the dye test, and several clinicians prefer this test if only one is available. Feldman and Sabin,[10] who have had a great deal of experience with the intradermal test, believe that it is not useful for diagnosis because it bears no relationship to the titer of antibody and a negative skin test is encountered too often in the presence of antibody. Most authorities, however, feel that it is a good screening device even though absolute conclusions cannot be drawn from it in the individual case.

The methylene blue dye test for toxoplasmosis, developed by Sabin and Feldman in about 1948, depends upon the ability of a Toxoplasma-immune serum to inhibit the staining with methylene blue of the cytoplasm of the living Toxoplasma organisms. It is a quantitative test of the antibody concentration against Toxoplasma. It becomes positive early in the infection, and the titer rises during the active phases of the disease and fades over the years. It is a difficult, time-consuming test and is performed in only a few laboratories. During the chronic stage of toxoplasmosis, when retinochoroiditis is seen, the dye test titer may be and often is low. The titer of the patient's serum may be 1:8, 1:16, or 1:32,000, and any of these is significant. To set a certain minimum titer requirement for uveitis such as Sabin [11] suggested, of 1:256, or as Woods [12] suggested, of 1:64 or 1:32, does not seem justified, because several years after an acute process the antibody concentration may fall. Therefore, even the lowest titers are indicative of past infections. Hogan [13] suggested that a rise of the dye test titer seen during uveitis is more convincing than a single low titer report. Repeated tests are not necessary clinically, although they are interesting for experimental purposes.

The correlation between the skin test and the dye test is fairly close. At the conference [13] in December, 1954, of the Parasitology and Tropical Medicine study section of the National Institutes of Health, Frenkel, Woods, Eichenwald, Ryan, Feldman, King, Owen, Passmore, Zimmerman, Jacobs, and others concluded that the skin test should be done as the initial test and then followed by the dye test when possible. In earlier writings Frenkel was of the opinion that the toxoplasmin skin test antigen would raise the dye test titer or incite an increased antibody response, but this is no longer believed and he feels now that a single toxoplasmin antigen injection would not change the titer sufficiently to confuse the test.

If one has made a presumptive diagnosis of acute toxoplasmic granulomatous uveitis with the correct clinical pattern, has ruled out other etiology, and has obtained a positive skin and dye test, one may wish to try drugs specifically effective against Toxoplasma organism, as well as symptomatic therapy. Eyles [14-15] and his co-workers demonstrated a synergistic effect of sulfadiazine and pyrimethamine in the treatment of experimental toxoplasmosis in the mouse. Since then, Ryan,[16] Woods, Naquin,[12] Cassady,[17] Burnham,[18] Perkins and Smith,[19] and others have treated many patients with uveitis with antitoxoplasmic drugs. Severe acute systemic infections have also been successfully treated with pyrimethamine and sulfonamides.

Some ophthalmologists have reported no observable improvement in toxoplasmic uveitis after pyrimethamine and sulfonamides had been administered. In two of these reports such small doses of pyrimethamine were used that it would have been unusual if improvement had occurred. To be effective, adequate therapeutic dosage should be administered, such as 25 mg. of pyrimethamine and 1 gm. of combined sulfacetamide, sulfadiazine, and sulfamerazine per 60 lb. of body weight in 24 hours. These drugs, especially the pyrimethamine, are folic acid depressants and cannot be used unless frequent blood studies are done during treatment.

The pathogenesis of the inflammatory changes in the eye is dependent upon the release of antigen or proliferative organisms by the breakdown of Toxoplasma cysts. Corticosteroids should be administered along with the pyrimethamine and sulfonamides to allay the hyperergic reaction and to prevent the reencystment of the organisms. Pyrimethamine and sulfonamide are effective against the proliferative forms and ineffective against the encysted organism. This treatment gives no protection against recurrence of the uveitis. If 25 mg. of pyrimethamine and 1.0 gm. of sulfonamide per 60 lb. of body weight is tolerated, it is

administered along with a moderate dose of corticosteroid, such as 20 mg. of prednisolone. This therapy is continued for 10 days to 2 weeks in divided doses. The dosage is then reduced one-half and continued, if it can be tolerated, for at least a month, depending upon tolerance.

The dramatic response to this therapy is as marked as that of tuberculous uveitis to isoniazid. The vitreous clears, the uveitis subsides, and the retinitis, obscured by the vitreous haze, becomes visible. The improvement is most marked within the first week of treatment. The vitreous opacities persist and do not entirely clear for several weeks. The retinal lesion heals, pigment appears, and the vision improves.

The pyrimethamine and sulfonamide may not be tolerated, causing nausea, anorexia, general weakness, or toxic depression of hematopoiesis. The potential danger of this treatment cannot be overemphasized. When Burroughs-Welcome introduced pyrimethamine (Daraprim) as an antimalarial drug, a severe toxic bone marrow depression was said to result from a 25 mg. daily dose. To give 50 to 75 mg. along with sulfonamides, which are also toxic to the blood-forming organs, hazards a depression of platelet and white blood cells. Platelet and WBC counts are recommended every few days during the early administration of these drugs. If depression occurs, the drugs should be stopped. The red cells, having a longer life, are the last to show alteration and may appear normal after the platelets disappear. Purpura and agranulocytosis are due to the folic-acid-depressant effects of the drugs. If toxic effects are recognized early, discontinuance of the drugs allows the bone marrow to start functioning, but, if late, administration of folic acid or corticotropin (ACTH) administered intravenously may be required to restore activity to the blood-forming organs.

New tests for the disease are being developed that may be valuable in helping us to determine whether uveitis is caused by Toxoplasma. O'Connor [20] recently described an agar-diffusion technique. He was able to find antitoxoplasmin precipitins in the aqueous humor in four patients with toxoplasmic uveitis. A toxoplasmic granulomatous uveitis cannot be diagnosed definitely from positive skin and dye tests. They permit only a presumptive diagnosis at the present time.

The method of transmission of this disease is still a mystery, according to Jacobs.[3] Although toxoplasmosis is widespread, direct animal contact between litter mates does not spread the infection. Intestinal lesions suggest that the gastrointestinal tract may be the portal of entry. No transmission by ticks or by infected mosquitoes could be produced. According to Jacobs [3] and Feldman,[21] the disease is prevalent in warm moist areas, more in southern than in northern Sweden, more in coastal areas of Mexico than in the high altitude around Mexico City. There is little or none in Iceland and Alaska, a considerable number of cases in Tahiti and its coastal regions. The eastern United States has a higher incidence than the western half of the country. These conclusions are based upon the sample serum dye test titers obtained from various areas. Toxoplasma organisms have been transmitted and studied in many experimental animals and can be transmitted by injecting a few organisms into almost any tissue. There is no tissue specificity. We are unable to determine by the antibody titer whether the infection is entirely healed. The dye test titer may fluctuate without apparent cause. The organism can be grown in tissue cultures, in chick embryos, or in white mice peritoneal cavities and can be preserved indefinitely at icebox temperatures.

More effective treatment than pyrimethamine and sulfonamides will be found. Hogan has been experimenting with other drugs, as have Eyles and others. One drug that showed promise was an antitoxoplasmic antibiotic substance, No. 534, a soil actinomycete found by Okami [22] and associates, but this has been abandoned. Much work remains to be done to classify the organism and to recognize its disease pattern, its mode of transmission, its pathogenesis, and its

true significance. We must find an effective treatment, especially one that will influence the organisms that remain encysted in the tissues. But with such tireless workers as Jacobs, Frenkel, Sabin, Feldman, Hogan, Eyles, Eichenwald, Siim, and Smith, who are still active in the investigation of toxoplasmosis, and others who have contributed so much or more, within another few years these investigators will make today's knowledge of toxoplasmosis seem meager or infinitesimal.

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REFERENCES

1. Markham, F. S.: Introductory Remarks, Ann. N. Y. Acad. Sc. 64:152-153 (July 5) 1956.

2. Wilder, H. C.: Toxoplasma Chorioretinitis in Adults: Preliminary Study of 41 Cases Diagnosed by Microscopic Examination, A. M. A. Arch. Ophth. 47:425 (April) 1952.

3. Jacobs, L.: Propagation, Morphology, and Biology of Toxoplasma, Ann. N. Y. Acad. Sc. 64:154-179 (July 5) 1956.

4. Siim, J. C.: Toxoplasmosis Acquisita Lymphonodosa: Clinical and Pathological Aspects, Ann. N. Y. Acad. 64:185-206 (July 5) 1956.

5. Feldman, H. A., and Miller, L. T.: Congenital Human Toxoplasmosis, Ann. N. Y. Acad. Sc. 64:180-184 (July 5) 1956.

6. Frenkel, J. K.: Pathogenesis of Toxoplasmosis and of Infections with Organisms Resembling Toxoplasma, Ann. N. Y. Acad. Sc. 64:215-251 (July 5) 1956.

7. Cathie, I. A. B.: The Non-Specificity of the Dye Test for Toxoplasmosis: With Particular Reference to Trichomonas Infection, Great Ormond St. J., No. 10, pp. 81-85 (Winter) 1955-1956.

8. Perkins, E. L., and Smith, C.: Preliminary Results of the Treatment of Uveitis with Daraprim, Proc. Roy. Soc. Med. 49:25-26 (Jan.) 1956.

9. Frenkel, J. K.: Dermal Hypersensitivity to Toxoplasma Antigens (Toxoplasmins), Proc. Soc. Exper. Biol. & Med. 68:634-639 (July-Aug.) 1948.

10. Feldman, H. A., and Sabin, A. B.: Skin Reactions to Toxoplasmic Antigens in People of Different Ages Without Known History of Infection, Pediatrics 4:798-804 (Dec.) 1949.

11. Sabin, A. B.: Human Toxoplasmosis with Special Reference to Intraocular Inflammation: A Critical Review, Am. J. Ophth. 41:600-606 (April) 1956.

12. Jacobs, L.; Naguin, H.; Hoover, R., and Woods, A. C.: A Comparison of the Toxoplasmin Skin Tests, the Sabin-Feldman Dye Tests, and the Complement Fixation Tests for Toxoplasmosis in Various Forms, Bull. Johns Hopkins Hosp. 99:1-15 (July) 1956.

13. Hogan, M. J.: Ocular Toxoplasmosis: Clinical and Laboratory Diagnosis; Evaluation of Immunologic Tests; Treatment, A. M. A. Arch. Ophth. 55:333-345 (March) 1956.

14. Eyles, D. E., and Coleman, N.: Synergistic Effect of Sulfadiazine and Daraprim Against Experimental Toxoplasmosis in the Mouse, Antibiotics & Chemother. 3:483-490 (May) 1953.

15. Eyles, D., and Coleman, N.: An Evaluation of the Curative Effects of Pyrimethamine and Sulfadiazine Alone and in Combination on Experimental Mouse Toxoplasmosis, Antibiotics 5: 529-539 (Oct.) 1955.

16. Ryan, R. W.; Hart, W. M.; Culligan, J. J.; Gunkel, R. D.; Jacobs, L., and Cook, M. K.: Diagnosis and Treatment of Toxoplasmic Uveitis, Tr. Am. Acad. Ophth. 58:867-884 (Nov.-Dec.) 1954.

17. Cassady, J. V.; Culbertson, C. S., and Bahler, J. W.: The Etiology of Retinochoroiditis and Uveitis: Importance of the Dye (Methylene Blue) Cytoplasm-Modifying Antibody Test for Toxoplasmosis, A. M. A. Arch. Ophth. 54:28-36 (July) 1955.

18. Burnham, C. J., and Buerman, V. A.: Toxoplasmic Uveitis: Treatment with Pyrimethamine and Sulfadiazine, Am. J. Ophth. 42:217-227 (Aug.) 1956.

19. Perkins, E. W.; Smith, C. H., and Schofield, P. B.: Treatment of Uveitis with Pyrimethamine (Daraprim), Brit. J. Ophth. 40:577-586 (Oct.) 1956.

20. O'Connor, G. R.: Anti-Toxoplasma Precipitins in Aqueous Humor: New Application of the Agar-Diffusion Technique, A. M. A. Arch. Ophth. 57:52-57 (Jan.) 1957.

21. Feldman, H. A., and Miller, L. T.: Serologic Study of Toxoplasmosis Prevalence, Am. J. Hyg. 64:320-335 (Nov.) 1956.

22. Okami, Y.; Utahara, R.; Oyagi, H.; Nakamura, S.; Umezawa, H.; Yanagisawa, K., and Tsunematsu, Y.: The Screening of Anti-Toxoplasmic Substance Produced by Streptomycete and Anti-Toxoplasmic Substance No. 534, J. Antibiotics, Ser. A 8:126-131 (Aug.) 1955.

Annual Reviews

Ophthalmic Pharmacology and Toxicology

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This review covers the relevant literature published during the period April, 1956, to April, 1957* During this time there have been no really outstanding developments in ophthalmic pharmacology, and the preoccupation with acetazolamide (Diamox) shown in the previous year has definitely abated. However, there seems to have been an increased interest in testing the effects of other drugs on the intraocular pressure, including ganglion-blocking agents, tranquilizers, natural alkaloids, miotics, and vasoconstrictors. A well-sustained interest has been evident in the responses of retinal and choroidal vessels to drugs and in the therapeutic applicability of steroid hormones and of antibacterial substances.

One of the most notable observations concerning the effects of drugs on the eye during the period under review comes under the heading of toxicology; this has been the discovery of retinal degenerative changes in numerous patients receiving a new tranquilizing drug. Of similar interest has been the development of retinal pigmentary changes in animals given a new group of chemotherapeutic agents. A former widespread interest in study of the relationship of oxygen to development of retrolental fibroplasia appears to have subsided with general agreement on the great danger of oxygen administration to premature infants.

In the present review, as in last year's review of ophthalmic pharmacology and toxicology, it is not my intent to provide an exhaustive or all-inclusive compendium but to summarize and correlate the developments of the past year in a simple and convenient form.

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* The journals surveyed included *Acta ophth., Acta pharmacol. et toxicol., Acta physiol. scandinav., Am. J. Ophth., Am. J. Physiol.,* A. M. A. ARCH. OPHTH., *A. M. A. Arch. Indust. Health., Ann. ocul., Arch. exper. Path. u. Pharmakol., Ber. deutsch. ophth. Gesellsch., Brit. J. Indust. Med., Brit. J. Ophth., Brit. J. Pharmacol., Docum. ophth., Helvet. physiol. et pharmacol. acta, J. A. M. A., J. Gen. Physiol., J. Pharmacol. & Exper. Therap., J. Physiol., Klin. Monatsbl. Augenh., New England J. Med., Ophth. Lit., Ophthalmologica, Pharmacol. Rev., Proc. Soc. Exper. Biol. & Med., Survey Ophth., Tr. Am. Acad. Ophth., Tr. Am. Ophth. Soc., Tr. Ophth. Soc. U. Kingdom, von Graefes Arch. Ophth., Zentralbl. ges. Ophth.*

Ophthalmic Pharmacology

Influence of Drugs on the Intraocular Pressure.—In treatment of glaucoma, acetazolamide has maintained its important position for the third year since its introduction into ophthalmology. The clinical indications and manner of use in acute angle-closure, as well as in chronic open-angle, glaucoma and in glaucoma secondary to uveitis have become familiar to most ophthalmologists. Serious misuse has been evident only in cases of angle-closure glaucoma in which there has been a failure to perform iridectomy; in these cases peripheral anterior synechias can become well-developed during a period of false sense of security while acetazolamide has depressed intraocular pressure by partial inhibition of aqueous formation and yet portions of the angle of the anterior chamber may have

failed to reopen. It has become apparent that reduction of intraocular pressure by acetazolamide in acute angle-closure glaucoma provides favorable conditions for performance of iridectomy but that the drug is no safe substitute for the operation.

Experimentally, there has been little advance in elucidating the mechanism by which acetazolamide lowers the rate of formation of aqueous humor beyond what was understood a year ago. In an informal conference in February, 1957, several of the more active investigators of this problem (Ballintine, Becker, Green, Kinsey, and Langham) found themselves in agreement on the following actions of acetazolamide: 1. It lowers intraocular pressure in both normal and acidotic rabbits. 2. It decreases the formation of aqueous humor. 3. Its effect on intraocular pressure is independent of renal action. 4. It decreases the excess of bicarbonate and lowers the pH in the aqueous humor of rabbits. 5. Its action is associated with an increase in ascorbate concentration in the aqueous humor, particularly in the posterior chamber. 6. The same changes accompany acidosis induced by administering ammonium chloride to rabbits. Among these investigators there persist some differences in estimate of duration of effect of a single dose of acetazolamide, Langham having evidence of only a transitory depression of inflow, based on measurement of fluorescein-appearance-time in rabbits given urethan,[76] and Becker having evidence of longer-sustained depression of inflow, with partially compensatory increase in resistance to outflow, based on tonography and fluorescein appearance-time obtained by a different technique in unanesthetized rabbits. Reports from other investigators have not been entirely in agreement with the conclusions reached by the group mentioned above. Kleinert, for instance, has contended that acetazolamide does not decrease the flow of aqueous humor because he was unable to detect any change in the appearance of the episcleral vessels in patients when the intraocular pressure was lowered by this drug,[70] and Hodgson, in preliminary studies, did not find a change in ascorbate concentration in the aqueous humor.[52] Another investigator did not find what he considered to be a significant increase in fluorescein-appearance-time in rabbits given acetazolamide.[14] There has, however, been no serious basis as yet for questioning the conclusions listed earlier in this paragraph. Unfortunately, the more fundamental aspects of the question of how acetazolamide suppresses aqueous formation have yet to be worked out, e. g., how the net water movement from blood to aqueous humor is reduced.

While I am discussing acetazolamide primarily in connection with its influence on intraocular pressure, there are some other effects of the drug to be noted. For instance, it has been determined in rabbits which have been given an injection of horse serum intravitreally and fluorescein intravenously that acetazolamide decreases the protein flare and the fluorescein concentration in the aqueous humor; furthermore, this effect has been found to parallel the lowering of pressure caused by the drug.[116] The influence of acetazolamide on the amount and rate of diuresis and on the sodium and potassium of blood and urine has been observed to parallel the influence of this drug on the intraocular pressure.[27] Again, the concentration of potassium in both blood and aqueous humor has been found to decrease after administration of acetazolamide to rabbits, but the significance of this change with respect to the intraocular pressure has still not been ascertained.[128]

The systemic and ocular toxicities of acetazolamide are gradually being evaluated clinically, and this is, of course, significant in relation to long-term administration to glaucomatous patients. It is reassuring to find that in addition to the single case of agranulocytosis previously reported in the literature only one more case has been added.[132] This is apparently a rare idiosyncratic reaction to the drug.

No new serious complications of acetazolamide treatment have come to light in the

past year, and it is generally appreciated that, apart from the unpleasant side-effects of reversible paresthesias and anorexia, the complication to be most seriously considered in deciding on a protracted course of treatment with this drug is the possibility of precipitating urinary calculi. No untoward effect has been found on vision as measured by refraction[93] and testing of dark adaptation,[95] except for two rare cases of transient acute myopia,[6,9] in one of which there was noted an associated shallowing of the anterior chamber and rise of pressure to 40 mm.[6]

Experimental testing of drugs other than acetazolamide for influence on intraocular pressure in animals and evaluation of new drugs in glaucomatous patients seems to be receiving increasing attention from investigators in recent years, possibly because the prospects for achieving worth-while results have been made more attractive by the example of acetazolamide. In most instances, underlying the selection of drugs for testing there has been some concept of how the formation and outflow of aqueous humor might be controlled. Inevitably, these working concepts must be largely speculative at the present stage of understanding of the physiology of ocular hydrodynamics. For instance, with the thought that some control might be exerted by the nerve supply to the eye and by the central nervous system, tests have been made of the influences of ganglion-blocking agents and tranquilizing drugs. (It may be recalled, however, in connection with the testing of ganglion-blocking agents on intraocular pressure that denervation and central stimulation experiments have succeeded in demonstrating only transient influences of innervation on this pressure.)

The ganglion-blocking agent hexamethonium chloride (Depressin), administered intravenously or intramuscularly to patients, was found, as reported previously, to cause a transient decrease of intraocular pressure; this averaged 5.2 mm. for normal and 13.2 mm. for glaucomatous eyes.[19,112] The blood pressure also fell, but probably not enough to cause the change observed in intraocular pressure. Tonography revealed no change in facility of outflow, and it appears probable, therefore, that the formation of aqueous humor was temporarily depressed. Interestingly, the injection of hexamethonium retrobulbarly in quantity sufficient to block the ciliary ganglion and induce mydriasis caused no change in intraocular pressure, and this suggests that the ganglia of the sympathetic supply to the eye may have been a more significant site of attack than the parasympathetic ganglia when the pressure was lowered following systemic administration.[112]

Phentolamine (Regitine), which is a drug employed clinically to block hypertensive actions of circulating epinephrine and arterenol, caused a decrease of intraocular pressure and rate of aqueous formation (determined tonographically) for at least two hours in rabbits which had been given the drug parenterally.[81]

On the other hand, oral administration of the ganglion-blocking agents chlorisondamine (Ecolid) and mecamylamine (Inversine) to patients failed to lower the intraocular pressure, even though they were given in doses sufficient to induce mydriasis and cycloplegia.[17] Similarly, little influence on intraocular pressure was observed when pentolinium bitartrate (Ansolysen) was given orally, and only a slight transient lowering was found after injection.[17,59,103] Surprisingly, patients who had received a dose of 10 to 20 mg. of pentolinium on two successive days were found by tonography to have a considerable decrease in facility of aqueous outflow, and, since the intraocular pressure was not much altered, it appeared that the rate of aqueous formation must also have been depressed.[114] It was possible that the drug affected both facility of outflow and rate of formation, or that it affected only one of these factors and that the other responded through some compensatory or homeostatic mechanism tending to keep the intraocular pressure

constant. It does not seem that the precise mechanism could be established from the evidence at hand, but the assumption has been made that the formation of aqueous humor was first affected.[114]

Chlorpromazine (Thorazine, Megaphen, Largactil), which has both peripheral and central actions, is, as previously reported, effective in lowering the intraocular pressure for several hours when administered systemically, but it has no effect on pressure when given locally.[31,74,102,103] This drug, like hexamethonium, appears to depress formation of aqueous humor rather than affect the facility of aqueous outflow.[31] Similarly, there is evidence to suggest that this effect may be achieved through sympatholysis, but, again, the influence on intraocular pressure is transitory even during repeated administration of either drug. Despite the short duration of effect, practical use may be made of chlorpromazine as an aid in relief of acute glaucoma in patients immediately prior to operation (e. g., 50 mg. slowly intravenously 20 to 50 minutes preoperatively).[48]

The tranquilizing drugs reserpine and meprobamate (Miltown) have been tested for effect on the intraocular pressure of rabbits.[103] Reserpine had no appreciable effect, although it induced miosis, ptosis, and lethargy. Meprobamate caused a transient lowering of pressure only when very large doses were given (400 mg. per rabbit), and mydriasis was induced.

Another group of drugs which most obviously affect brain function have been tested for effect on intraocular pressure with the supposition that they may exert some influence through the central nervous system, although the postulated central control of intraocular pressure has not yet been conclusively demonstrated. A group of 16 natural alkaloids from opium, Corydalis, and other sources were tested by intravenous injection in rabbits, and tonometric determinations of intraocular pressure were made.[82,84] In most instances the pressure either increased or decreased from 5 to 11 mm. immediately following the injections, with no relation to pupil size. In the case of sanguinarine, a rise of 17 mm. was observed. The pressures were usually back to normal within an hour. No evidence was obtained to establish the site or mode of action, but in the case of sanguinarine the rise in pressure induced by experimental feeding to monkeys has been attributed to structural alterations in the angle of the anterior chamber.[78,88]

Drugs which alter the tone of the extraocular muscles may influence the intraocular pressure for short periods, at least until a compensatory change in intraocular fluid volume has taken place. The influence of the extraocular muscles on the pressure is of little significance in relation to medical treatment of glaucoma, but it is of much significance in relation to the condition of the eye at the time of intraocular surgery, either for glaucoma or for cataract extraction. Many drugs and numerous procedures have been investigated for lowering the pressure in the eye preoperatively. Certain drugs, succinylcholine (Anectine) and decamethonium, which might have been expected to have a favorable action because they relax skeletal muscle, have the opposite effect on extraocular muscle, causing tetanic contraction and temporary elevation of intraocular pressure. Both drugs have already been well investigated, and in the period under review electromyographic studies and experiments on excised human extraocular muscle have been presented substantiating previous conclusions.[54,55,85] The peculiar tetanic contraction of extraocular muscle has been attributed to the contraction of the so-called slow fibers, which are thought to be pharmacologically similar to fibers of the rectus abdominis of frogs. The response of extraocular muscles can be abolished by general anesthesia or curare.

The desired preoperative relaxation of extraocular muscles and satisfactory lowering of intraocular pressure in patients have been obtained by administration of guaiacolglycerin ether.[55] A 5% solution of this sub-

stance (Reorganin) was administered intravenously, 20 ml. shortly before operation, along with ordinary oral dosage of chlorpromazine. This, even without retrobulbar injection of anesthetic, gave good relaxation of the patient, paralysis of lid muscles, and 3 to 8 mm. decrease of intraocular pressure in 5 to 20 minutes. This medication has been recommended in preparation for cataract extraction.

Thiopental given intravenously to patients was found to reduce the pressure in glaucomatous eyes by about 19 mm. (average) in 20 mintes.[112] By tonography this appeared to be due to an increase in facility of outflow.

Studies on miotic parasympathomimetic drugs in the period under review have been concerned with a variety of both old and new drugs. Tests of several familiar direct-acting and several cholinesterase-inhibiting miotics have established that all these substances induce only slight decrease of pressure in normal human eyes, the most influential being 0.2% isofluorophate (DFP, diisopropyl fluorophosphate, Floropryl), which decreased the pressure by 3 to 5 mm. mercury.[83] On the other hand, a correlation has been found between the tonographically determined resistance to aqueous outflow of various normal human eyes and their responsiveness to physostigmine (Eserine); physostigmine had little influence on the outflow of those eyes having the lowest resistance but did cause a decrease in resistance to outflow in those having highest resistance.[140]

A few new parasympathomimetic drugs have been developed and tested, and, as might be expected from their fundamental similarities and common mode of action, none has been found or is likely to be found to exceed significantly the effectiveness of known miotic drugs in reducing intraocular pressure. The principal purpose in the investigation of new drugs in this category is, therefore, to discover substances having advantages of lower toxicity, less tendency to sensitize, and improved stability, while maintaining maximum effectiveness in lowering intraocular pressure. The miotic drugs which are currently employed clinically have well-known limitations in these regards. Favorable results have been obtained with a new compound comprised of two neostigmine molecules joined together by a long carbon chain, decamethylene-bis-(N-methylcarbaminoyl-*m*-trimethylammonium phenol).[41] This drug, employed as a 1% aqueous collyrium, is a long-acting inhibitor of cholinesterase, providing miosis for 5 to 10 days. In the treatment of glaucomatous patients it has been found to be similar to isofluorophate in both intensity and duration of its effect on the intraocular pressure. In a series of 53 patients no sensitivity reaction or significant systemic intoxication was observed. Still another effective inhibitor of cholinesterase has been tested on rabbit eyes for miotic activity and has been found to have the same intensity and duration of action as neostigmine, even when applied at only one-tenth the concentration of the latter; no reports have been made yet on the clinical attributes of this compound (4, 4'-oxy-bis-phenacylpyridinium; Lilly 21315).[49] A variant of tetraethylpyrophosphate (TEPP) in which sulfur is substituted for one oxygen (giving tetraethylmonothiopyrophosphate) has been tested clinically in treatment of glaucoma in the Soviet Union.[135] This substance apparently has properties similar to those which have been reported for TEPP and must similarly be employed in oily solution; it is not evident whether it has as great a tendency to cause sensitization.

Not uncommonly attempts have been made to obtain greater effectiveness in control of glaucoma by employing combinations of miotic drugs despite some recognized competitive interferences among them. The result in some instances is an actual lessening of the effectiveness of the stronger drug. In the case of mixtures of a diethyl *p*-nitrophenyl phosphate (Mintacol) and neostigmine (Prostigmin), however, tests of inhibition of cholinesterase in homogenized

cattle iris have not revealed a degree of interference which would be clinically significant.[81]

An interesting study has been made of the distribution of physostigmine in the eyes of rabbits after a 2% solution is dropped in the conjunctival sac.[118] By assay of the cholinesterase-inhibiting activity of the various tissues and fluids, it was found that physostigmine disappears from the surface of the eye and from the aqueous humor in 10 to 15 minutes but that it is detectible in the cornea for 4 hours and in the iris and ciliary body for about 8 hours. The lens and vitreous did not take up physostigmine appreciably and did not therefore constitute a reservoir for the drug. The duration of miosis corresponded approximately to the time of persistence of physostigmine in the iris itself.

Various vasoconstrictor drugs have proven clinically useful in control of glaucoma either in conjunction with miotics in primary glaucoma or in combination with mydriatic-cycloplegics and allied drugs in treatment of glaucoma secondary to uveitis. It has been determined that epinephrine and chemically related drugs lower the intraocular pressure by decreasing the rate of formation of aqueous humor and that this effect may persist for many hours, much longer than the associated brief vasoconstrictor action. The mechanism of this inhibitory action is unknown, but it is generally postulated to involve a disturbance of the metabolism of the ciliary body. In this regard a recent extensive review of the metabolic effects of epinephrine and related amines indicates that at a very fundamental level much is being learned which may eventually provide a basis for understanding the action of these substances in control of glaucoma.[35] Acutally, no reference is made to the eye problem in the above-mentioned review, and this suggests that ophthalmic investigators have yet to investigate the action of epinephrine from a really fundamental standpoint.

Clinically, among substances related to epinephrine and similarly useful in treatment of glaucoma, recent observations have been reported on Effortil (1-[3-oxyphenyl]-1-oxy-2-ethylamino-ethane),[71] on epinephrine,[101] and on isoproterenol (Isuprel).[79] The first two substances have less vasoconstrictor, mydriatic, and pressure-lowering effect than epinephrine when dropped on the eye in equal concentrations; the third causes vasodilatation and no mydriasis but has some pressure-lowering action. Trial of isoproterenol in glaucomatous patients indicated that 0.5% solution was useful in conjunction with pilocarpine but that 1% solution caused excessive irritation of the eye and lids.[79] No advantage over epinephrine was demonstrated.

The principal hazard associated with the use of sympathomimetic drugs is the possibility of causing an abnormally narrow angle to close as a result of mydriasis. Systemic toxic effects rarely constitute a hazard from these drugs when they are applied to the surface of the eye, but one instance of a great rise in blood pressure and associated subarachnoid hemorrhage is reported to have been caused by 10% phenylephrine hydrochloride (Neo-Synephrine) in a cotton pack placed in the conjunctival sac.[92] That this is a rare complication was confirmed by instillation of the same solution into the conjunctival sac of a series of both normal and hypertensive persons without more than a 10 mm. change in blood pressure resulting.

A superficial similarity to the ocular-pressure-lowering action of epinphrine-like drugs is observed with the antidiuretic hormone vasopressin (β-hypophamine) which is a strong vasoconstrictor and has been found to lower intraocular pressure by depressing aqueous formation.[12] This substance acts locally upon application as drops and suppresses aqueous formation for something less than four hours in both normal and glaucomatous human eyes. Unfortunately, clinical application is limited because the eye rapidly becomes unresponsive to the drug upon repeated application. How this drug interferes with aqueous formation is still unsettled.

Among the many drugs which influence the intraocular pressure are some which cause a transient increase in pressure. One substance which causes a rise in pressure in rabbit eyes when injected subconjunctivally is calcium phosphorylcholine chloride; this substance has also been recommended for clinical topical application in cases of hypotony, with claims of beneficial results.[20] The induction of miosis, vasodilation, and transient pressure rise in rabbit eyes by this substance is consistent with the known effects of calcium chloride, and calcium chloride constitutes a considerable proportion of calcium phosphorylcholine chloride. On the other hand, the phosphorylcholine portion of the compound is known to have only a low order of pharmacologic activity, which seems inconsistent with the effects on the eye imputed to it. A more critical investigation is needed, both experimental and clinical.

Corticotropin (ACTH) has been found to cause a slight sustained rise in intraocular pressure in rabbits when injected intramuscularly daily, and in one patient under treatment for sarcoidosis a similar effect has been attributed to this hormone.[26] Reports relating a rise in intraocular pressure to treatment with adrenal corticosteroids have appeared previously, but in most studies of these hormones no effect on pressure has been found.

Mydriatic-Cycloplegic Drugs.—In treatment of uveitis and in refraction the drugs in this category are in constant demand, and any improvement in desired clinical attributes is of practical significance. Notable advantages have been found in a new parasympatholytic drug, oxyphenonium bromide (Antrenyl), which has been evaluated in 75 patients requiring mydriasis because of ocular inflammation due to a variety of causes.[37] Most significant was the fact that all of these patients had previously become allergic to atropine and some were sensitive to scopolamine (hyoscine), lachesine, hyoscamine (duboisine), and homatropine; yet no cross sensitization to the new drug was found, and only one patient acquired a sensitivity to it. All except two of the patients tolerated the drug well during treatment periods of 1 to 51 weeks. In all instances, at least as wide mydriasis was obtained as from atropine when the new substance was applied four times a day as a 5% solution incorporating 1:5000 benzalkonium chloride. Standing in contrast with the foregoing informative and useful study is another recently published test of mydriatic-cycloplegic compounds on human eyes in which no comparison was made with other drugs and no identification was given of the substances tested except by a manufacturer's code number.[57]

Underlying the development of new parasympatholytic drugs are fundamental studies of the relationship of chemical structure to efficacy in blocking the sites of action of acetylcholine in tissues.[80] In such studies measurement of mydriatic activity in mice has commonly provided the means for quantitative evaluation of atropine-like parasympatholytic action and also has served for convenient assay of parasympathetic ganglion-blocking activity of hexamethonium analogs.[16]

A comparison in human eyes of the cycloplegia induced by homatropine and the loss of accommodation occurring naturally in presbyopia revealed a difference in mechanism. In drug-induced cycloplegia the ratio of accommodative convergence to accommodative stimulus increases, but it does not increase in presbyopia.[30]

An interesting miotic-mydriatic antagonism between morphine and its antagonist nalorphine (Nalline) is reported to be under consideration by law-enforcement agencies as a test for addiction to morphine and related narcotics.[147] Morphine taken systemically causes miosis through action on the central nervous system, while nalorphine counteracts both the central nervous depression and the miosis. Nalorphine alone, on the other hand, itself causes some miosis. A tendency to increase the size of the pupil is said to be obtained only when nalorphine

is working in antagonism to morphine or similar narcotics.

Corticosteroids and Other Anti-Inflammatory Agents.—The value of cortisone and related substances in treatment of nonbacterial and nonviral inflammatory diseases of the eye has become so well established that publications on the subject now consist principally of reviews [21,33,67,80] or of reports on trials of new derivatives.[1,42,67,131] The role of parenteral cortisone and corticotropin in treatment of temporal arteritis with visual loss has been examined through an analysis of the literature and study of six new cases, with the conclusion that under treatment with these substances complete blindness is less likely to result.[13] Clinical experiences in treatment of a variety of inflammatory conditions of the eye has provided evidence for superiority of topically applied hydrocortisone over cortisone in some cases [67] and for superiority of prednisone and prednisolone over cortisone and hydrocortisone in other instances.[42,131] The incidence of the side-effects of edema and moon-face were found to be approximately the same in systemic treatment of ocular disease with these different agents. Attention has been called to the discomforting effect on the eye of corticosteroid preparations in which the material is in particulate form, and the suggestion is made that true solutions or finer particles might be less discomforting.[80]

Experimental studies have indicated that the reduction of inflammatory response occasioned by cortisone may be disadvantageous in the case of an invading injurious process or agent which could be circumscribed or localized by a natural protective reaction.[23] This may be the basis for an increase in the severity of Pseudomonas ulcers of the cornea in rabbits which has been observed when cortisone is administered.[125]

Experimental studies on rabbits have demonstrated striking benefit from treatment with cortisone following corneal injury by solutions of trimethylamine and colchicine.[35] Other well-designed experiments on rabbits have shown that the actual strength of corneal wounds, measured by the force required to disrupt them, is not significantly altered by systemic administration of cortisone.[36] From this latter study it was concluded that even though fibroblastic proliferation in the cornea is inhibited by cortisone, as established histologically by others, this does not affect the tensile strength of the tissue.

In addition to cortisone and related compounds, a number of other substances have been tested for treatment of uveitis. In certain instances these have been substances previously found beneficial in arthritis. One of these substances, phenylbutazone (Butazolidin), has been found in controlled experiments on rabbits to reduce the reaction to small lesions induced in the fundus by irradiation with high-intensity focused light.[94] The same drug administered in conjunction with aminopyrine to patients having a variety of ocular inflammations gave the clinical impression that this treatment promptly relieved acute inflammation and pain, especially in iritis, scleritis, and iridocyclitis.[127] In this study no systematic comparison was made with corticosteroid therapy, and it should be noted that phenylbutazone has a fundamental serious disadvantage of causing dangerous systemic toxic effects in about one out of four patients who receive this substance, and it is, therefore, generally held not to be a safe drug.[11]

Among other substances tried out for anti-inflammatory effect have been chlorpromazine and two sympathomimetic imidazoline derivatives. Chlorpromazine (Thorazine, Megaphen, Largactil) administered systemically to rabbits was found to have an inhibitory effect on horse-serum anaphylactic keratitis and on keratoiritis induced by croton oil.[75] Naphazoline (Privine, Strictylon) has been recommended with enthusiasm for treatment of a variety of ocular conditions, but the clinical evidence which has been presented does not seem to give much support to the claims.[100] A

related substance, tetrahydrozoline (Tyzine) has been tried out clinically as a sympathomimetic vasoconstrictor to blanch hyperemic conjunctivae.[45] In this application it has been found satisfactory, causing no appreciable anesthesia, no secondary hyperemia, and no pupillary effect at the concentrations employed; it is found to relieve itching.

Antihistaminic drugs seem to receive diminishing attention in the ophthalmic literature; one pharmacologic study has been reported in the period under review. In this study the isolated sphincter muscle of the iris was employed as a test object by means of which to evaluate the antagonistic action of substances against the smooth-muscle-constricting effect of histamine.[25] The sphincter iridis was employed in this study only because of a supposed semblance to vascular muscle, not because of any evidence involving the sphincter iridis in clinical ocular allergy.

Intramuscular injection of trypsin has been recommended for treatment of hemorrhages in and about the eye on the basis of clinical impression, but little controlled experimental work on this subject has been published. Recently, controlled tests of the influence of intramuscularly administered trypsin on experimental hyphema in guinea pigs have shown no benefit from this treatment.[64]

Chemotherapeutic and Antibiotic Substances.—Since it has been established that uveitis, particularly focal chorioretinitis, is caused in some cases by ocular infection with the Toxoplasma organism, there has been a search for specific means for treating this infection in patients. However, evaluation of potential therapeutic agents has been complicated by the fact that no reliable method has been developed for establishing clinically which cases of uveitis are actually caused by toxoplasmosis, because tests for systemic toxoplasmosis are positive in a considerable proportion of the population regardless of the presence of eye disease and no truly pathognomonic clinical features have been established. Because of these difficulties in clinical diagnosis, the testing of one potential therapeutic agent, pyrimethamine (Daraprim), has been carried out in cases of active uveitis without prior selection of cases, and comparison has been made with the results of administering an inert placebo to a like group of unselected cases.[105,121] Comparison of the rates of improvement in these two groups and examination of the relationship of therapeutic results to dye-test titers for systemic toxoplasmosis yielded the significant conclusion that no appreciable benefit was obtainable from pyrimethamine in cases having negative dye-test but that in about 25% of cases having dye-test titer of at least 1:4 a significantly more rapid improvement is obtainable with pyrimethamine than without.

Tuberculosis as a cause of ocular disease in patients presents some of the same difficulties for clinical diagnosis as does toxoplasmosis. However, experimentally an actual infection of the cornea of animals can be induced by direct innoculation with tubercle bacilli, and this provides a convenient preparation in which to test and view directly the effects of drugs such as isoniazid.[111] Since actual infections of the eye with tubercle bacilli are encountered rarely in patients, the results of this type of testing apply most directly to systemic tuberculosis and only indirectly to the clinical forms of ocular disease which are commonly attributed to a sensitization reaction to tubercle bacilli rather than to actual infection of the eye.

A new antibiotic, novobiocin, which has a wide range of action against both Gram-positive and Gram-negative bacteria, has been tested on rabbit eyes for toxicity and penetration.[119] It penetrates poorly through the epithelium or through the normal blood-aqueous barrier, but when these barriers are broken down it penetrates well in to the anterior chamber. It also penetrates well into the anterior chamber when injected subconjunctivally, but it does not reach the

vitreous in useful amount when injected in quantities which would be safe clinically.

Clinical evaluations of several antibacterial drugs, singly or in various combinations, have been reported. Neosporin, a mixture of polymixin B with bacitracin and neomycin, was found to be effective in local treatment of various infections of the anterior segment due to Gram-positive and Gram-negative bacteria and did not aggravate virus infections.[47] Clinical application of a still more complex commercial mixture containing antihistaminic and vasoconstrictor drugs in addition to antibiotics has been described, but without critical comparison.[106] In a comparison with oxytetracycline (Terramycin) in treatment of trachoma equal benefit was found for erythromycin applied in ointment form.[32] Administration of antibacterial drugs plus streptokinase parenterally prior to enucleation is reported to lessen the amount of edema which appears following the operation.[96]

Influence of Drugs on Retinal and Uveal Vessels.—An unusual number of studies on this subject have been reported in the past year, and several different techniques have been employed in these studies. An extensive and scholarly review has been presented of the literature concerning pharmacologic vascular effects, especially of the effects of a wide variety of drugs on intraocular vessels, but with little reference to their influence on intraocular pressure.[144] The various methods employed clinically and experimentally for evaluating retinal and choroidal vascular volume have been surveyed and cogently criticized.[15]

The influence of numerous drugs on the width of the retinal vessels has been determined by means of ophthalmoscopic measuring devices in rabbits and in normal human subjects.[123,142] From these observations it appeared that few drugs cause a visible widening of the vessels in the retina of the rabbit but that 1, 4-dihydrazinophthalazine (Nepresol) and closely related hydralazine (Apresoline) were the most effective, inducing vasodilatation of up to four hours' duration.[123] Acetylcholine, amyl nitrite, and hexamethonium had minor and relatively brief effect on the retinal vessels of the rabbit. In human subjects, on the other hand, numerous vasodilator drugs were found to cause increases in diameter of approximately 15% to 30% in the retinal arteries and 6% to 20% in the veins.[142] The drugs were all administered systemically, except one, which was injected retrobulbarly, and all but one caused a fall in systemic blood pressure of 20 to 40 mm. mercury. Whether the change induced in the retinal vessels was by direct action of the drugs or was a secondary response to a drop in systemic blood pressure was not ascertained. The most effective retinal vasodilator in human eyes was eupaverine, which at the same time caused the greatest fall of blood pressure. Only caffeine caused dilatation without lowering blood pressure. On the other hand, intravenous infusion of levarterenol caused an increase of retinal systolic and diastolic pressures in human eyes, and this was accompanied by a narrowing of retinal angioscotomas.[140] Interesting correlations have been observed between the retinal vascular effects and the molecular sizes of a series of organic nitrites; those of small size caused rapid transient dilatation, while those of large size had a delayed but persistent dilating action.[142] A combination of both types was recommended for prompt and lasting action for clinical use. No noteworthy evidence was presented to establish what place these retinal vasodilators might have in ocular therapeutics.

The influence of drugs on choroidal circulation has been studied in rabbit eyes by observation of the choroid through areas of sclera which have been rendered transparent by artificial dehydration, but this method permitted an adequate view only of the largest vessels. A great variety of drugs was tested by topical and systemic administration.[104,145] However, except for some constriction of long posterior ciliary arteries induced by potent vasoconstrictor drugs in high concentrations, all changes observed in

the circulation appeared to be secondary to alterations of the general blood circulation rather than to be direct responses of the choroidal vessels. By another method of investigation information was obtained on the combined blood volumes of retina and choroid. This method consisted of intravenous injection into cats of red blood cells which had been labeled with radioactive phosphorus; by placing a counter tube against the sclera and measuring the radioactivity of the underlying vascular bed an indication was obtained of the volume of blood therein.[15] This method does not distinguish between retinal and choroidal vascular beds, but presumably the choroidal contribution to the measurement predominates, because of the greater volume of the choroid. The influences of many drugs were tested, and by this method the most effective uveal vasodilators found were carbon dioxide administered by inhalation and aminophylline and tolazine administered by retrobulbar injection. A large increase in uveal blood volume could also be induced by paracentesis of the anterior chamber. Dilatation of the vessels of the iris in response to isofluorophate and to homatropine also have been studied by an India ink injection technique in eyes of rats.[62]

Influence of Drugs on the Electroretinogram.— The influence of epinephrine on the electroretinogram (ERG) of rabbits was investigated in an attempt to determine whether this drug has an influence on the pigment epithelium in mammals analogous to its effects in frogs.[115] Some changes were observed in the slow c-wave, and this was thought to be evidence of an effect on the pigment epithelium, but this was obtained only with doses of epinephrine far beyond the physiologic range. Another drug, nylidrin (Arlidin), was found to increase the b-wave of the ERG in patients, and this has been presented as evidence that the drug increases retinal blood flow; however, the basis for this interpretation was not explained.[60] A suggestive indication of functional similarities between retina and cerebral cortex was obtained in experiments in which ERG potentials were found to increase after parenteral administration of the hallucinogenic drugs lysergic acid diethylamide (LSD-25) and mescaline.[5]

Pharmacologic Influences on the Cornea. Recent advances in local anesthetics for surface application to the eye as well as for injection about the eye have been reviewed, and it has been pointed out that transient stinging or burning sensation such as is regularly caused by tetracaine (Pontocaine) has been minimized in newer agents, such as benoxinate (Dorsacaine); dyclonine (Dyclone); a preparation containing 2-dimethylamino-ethyl-3-amino-4-propoxy-benzoate hydrochloride, chlorbutanol, glycerin, and benzalkonium chloride (Ophthaine), and ambutoxate (Sympocaine).[107,126] For testing corneal sensitivity and the effectiveness of anesthetic agents an improvement over Frey hairs has been achieved by making use of a standard nylon thread in a device for varying its length and, thereby, its stiffness.[18]

An investigation of the influence of pilocarpine, cholinesterase inhibitors, atropine, and epinephrine on the electrical impedance of the epithelium of cattle corneas was carried out in an attempt to determine whether there is any relation between corneal permeability and the acetylcholine which is known to be normally present in high concentration in the corneal epithelium.[7] Actually, only slight alterations of impedance (employed as a measure of impermeability to ions) were induced by the drugs already mentioned. These drugs were applied with the assumption that they would have some influence on the acetylcholine of the epithelium. However, this study seems rather inconclusive, since no actual examinations of the acetylcholine of the epithelium is reported, nor any evidence whether it was in fact altered by the drugs applied.

Miscellaneous.—A widely advertised proprietary collyrium, Augentonicum Stulln, which was said to relieve ocular asthenopic symptoms by virtue of its digitalis content, was found to contain only a trace of digitalis

glycosides and to consist mostly of boric acid.[99] Tests on patients revealed that responses to placebo solutions of boric acid or of salt were as enthusiastic as to the proprietary mixture, revealing once again the psychotherapeutic effectiveness of some collyria.

Reports on treatment of retinal hemorrhages and vitreous opacities with a mixture of potassium iodide and nicotinamide[2] and treatment of senile macular degeneration with intravenous heparin indicate that these substances are beneficial,[113] but the results are hard to evaluate without a careful comparison with placebo-treated control groups. Similarly, a report of benefit to retinal arterial occlusions from administration of heparin was difficult for me to evaluate.[124] This particular work seems to be largely speculative, assuming retinal aterial occlusions to be caused by lipid materials associated with atherosclerosis but presenting no adequate evidence to establish this. Similarly, changes in the appearance of the fundus and reestablishment of circulation, which are credited to the lipid-clearing action of heparin, have not been adequately distinguished from the normal course of events.

A clinically useful application of saccharin to testing of the patency of lacrimal passages has been described.[87] This is based on the characteristic taste of saccharin, which is detectable by 97% of normal persons within an hour, usually sooner, after an innocuous 10% solution is dropped into the conjunctival sac.

Ophthalmic Toxicology

Cornea and Conjunctiva.—Most toxic disturbances of the cornea and conjunctiva are caused by direct contact with the injurious agent, and toxic disturbances of this part of the eye by the systemic route are relatively rare. Recently, however, a new instance of corneal injury by the systemic route has been reported, and this is of particular interest because it appears to be specific for man and chimpanzees, not affecting monkeys or dogs.[53] A drug known as Whipcide (3-methyl-1-pentyn-3-yl acid phthalate), which has proven exceptionally effective in dogs in treatment of whipworm, was administered to a series of human patients for the same purpose. All patients receiving a dose of 0.1 to 0.2 gm. per kilogram developed a uniform set of symptoms after about 12 hours, experiencing a burning sensation of the eyes progressing to severe photophobia and pain. The ocular lesions responsible were described as a "filmy keratitis," in some cases with small dense corneal opacities and in the most severe case with almost complete opacity of both corneas. Subsequently, all ocular abnormalities disappeared spontaneously in one to three weeks. The corneal lesions were, unfortunately, not described in sufficient detail to reveal which layer of the cornea was first affected or whether the opacities were caused by edema, cellular infiltrates, or other material. This would be interesting information. In this connection, it may be recalled that damage specifically to the endothelium of the cornea via the systemic route is known to be caused by ethylene dichloride, but only in canine species, not in primates. Thus the species specificity of these two unusual noxious agents are exact opposites.

Neovascularization of the cornea has been attributed to phenylbutazone (Butazolidin) in one case, but changes were observed in only one eye and this eye had sometime previously had corneal ulcer with folds in Descemet's membrane.[108] Deep in the stroma of this cornea a network of vessels appeared during phenylbutazone treatment for rheumatism, and it gradually disappeared after discontinuance of the medication. The evidence is suggestive, but more instances would be needed to establish this as a definite toxic manifestation. Treatment of arthritis with gold is well known to cause deposits of gold in the cornea and conjunctiva, and an additional case illustrating this condition has been presented, with biopsies of conjunctiva and skin demonstrating the presence of gold particles.[110] This condition of ocular chrysiasis rarely gives rise to

symptoms or causes other ocular complications, although gold treatment has in a few instances in the past been considered a cause of corneal ulceration and infiltration.

An experimental study of the reactions of the corneal stroma with a series of metal cations has shown that the tendency of various metals to induce corneal opacity when applied in approximately neutral solutions to rabbit eyes is in most instances correlated with the tendency of the metal to bind to the cornea and with the denaturing influence of the metal on this tissue.[44] The so-called denaturing influence was measured by loss of capacity of the stroma to absorb water and by loss of solubility of corneal mucoprotein in water. Although these latter physicochemical changes were rapidly induced, opacification of the cornea developed only after a latent period of as much as several hours and only in living animals. Furthermore, it was found that, if by appropriate treatment the noxious metals were removed from combination with the corneal stroma before the corneal opacity developed, the normal hydration properties and mucoprotein extractibility could largely be restored and opacification prevented. The most effective restorations of physicochemical properties were accomplished by means of edathamil (EDTA, ethylenediaminetetraacetate) following exposure to salts of yttrium, copper, and lead, and by means of sodium sulfosalicylate following exposure to beryllium sulfate. While these findings are potentially applicable clinically, it is evident that they are at present mainly of academic interest in relation to mechanisms of chemical injury.

In addition to those already mentioned, a considerable variety of actual or potential causes of chemical injury to the cornea have been noted in the past year. Among fishermen exposed in confined quarters to gases evolved by decaying oil herrings, 31 cases of bilateral keratitis epithelialis were observed.[38] Severe discomfort developed several hours after exposure, but all recovered spontaneously, except for two cases which had deep keratitis and scarring. The gases were found to be composed principally of ammonia, hydrogen sulfide, and methylamines. Attempts to identify the component responsible for the keratitis epithelialis by testing a variety of nitrogenous compounds on eyes of rabbits cast principal suspicion on the methylamines. However, hydrogen sulfide was not included in these tests, although it was found present in significant amounts in the atmosphere which injured the patients and a very extensive literature on the subject has thoroughly established that hydrogen sulfide characteristically causes keratitis epithelialis with an onset several hours after exposure. It seems to me that hydrogen sulfide was not given adequate consideration in connection with the injuries from decomposed fish.

Among the other causes of corneal injuries reported recently, butyl alcohol vapor has again been the cause of vacuolar keratitis; this time in the employees of a plastics factory, where it was utilized as a solvent.[61] Glycidol, which is an epoxy relative of glycerin, and several glycidol ethers have been noted to be potentially injurious to the eye even in vapor form, but because of the warning provided by ocular discomfort even at low concentrations it is probable that excessive industrial exposures to the vapor will not occur.[50] Evaluations of the toxicity of other industrial solvents indicated that vapors of butyl cellosolve (2-butoxyethanol) cause only mild eye irritation in industrial use[29] and that no more than slight corneal epithelial injury in rabbits is caused by splash contamination with benzene, toluene, xylene, ethylbenzene, diethylbenzene, isopropylbenzene, styrene, methylstyrene, or vinyl toluene.[143] Dimethylformamide applied full strength caused moderate, but apparently not severe, injury.[90] Airborne dust of lithium hydride, a highly reactive chemical, causes irritation and inflammation of the eyes, but only at concentrations which also cause strong respiratory irritation.[122] A series of barium salts of organic sulfur compounds which are employed as additives to lubricating oils because of their detergent properties have been ascertained by tests on

rabbits not to constitute an eye hazard.[141] Comparisons have been made of the tendency of a series of organic acids, aldehydes, ketones, and alcohols to induce edema when in contact with rabbit conjunctiva, but no observations were reported on the cornea, which would be of greater interest from the ophthalmic viewpoint.[77] In the course of investigation of colchicine as a possible agent for treatment of herpes simplex keratitis it was found that 1 drop of a 1% solution would cause serious clouding of the corneal stroma in human and rabbit eyes, requiring some weeks to clear.[38]

In treatment of severe chemical injuries of the cornea, following the regular initial decontamination procedures, nothing new has been found to equal local application of corticosteroids. The effectiveness of cortisone has again been demonstrated, this time in treatment of experimental injuries from trimethylamine and colchicine.[38] A suggestion has been made that in first-aid treatment of alkali-burned corneas the irrigating solutions might advantageously be employed cold, since pieces of rabbit cornea are found to dissolve more slowly in solutions of sodium hydroxide when the solutions are cooled.[120] It seems to me that there are additional factors to be considered and evaluated experimentally before this suggestion is put into general practice, but the principle may well have merit.

Anterior Chamber and Iris.—Following experimental injury of the cornea in rabbits by hydrocholoric acid it has been established that the ascorbate and lactate concentrations of the aqueous humor in the anterior chamber become subnormal for about three days; yet the ascorbate in the posterior chamber remains at its normal high level relative to the blood. Now, by measurement of the distribution ratio of *p*-aminohippuric acid (PAHA) between plasma and aqueous at steady-state and the disappearance rate of PAHA from the anterior chamber, it has been determined that the permeability of the blood-aqueous barrier of the iris is increased following injury of the cornea by hydrochloric acid.[4] This increased permeability serves to explain the tendency of the ascorbate and lactate concentrations of the aqueous humor in the anterior chamber to approach the concentrations in the blood at a greater than normal rate in the injured eyes. The significance of this alteration of the dynamics of the aqueous humor relative to reparative processes in the cornea remains to be determined.

The anterior chamber of rabbits has been utilized as a convenient location in which to study the induction of granulomas by silica.[138] Although the stimulus for this work was an interest in the pathogenesis of pulmonary silicosis, and the anterior chamber of the eye was utilized only because this location permits direct view of experimental lesions, the results have some ophthalmologic interest. In this study, approximately 2γ of quartz dust, composed mostly of particles of 2μ to 3μ in diameter, were injected into the anterior chamber, where they sank to the lowest portion of the angle. In other rabbits, brick dust and other mineral dusts were injected for comparison. The primary reaction of the eyes was the same in each case, prompt formation of a fibrinous exudate and beginning resorption of the exudate in a few days. The peculiar properties of quartz dust became evident later. In the quartz-injected eyes the fibrin did not become completely absorbed as it did in the other eyes, and in three to five weeks a secondary inflammatory reaction appeared in the quartz-injected eyes, with organization of the exudate in the lower iridocorneal angle to form a fibrotic nodule. Interestingly, quartz particles which were inadvertently left within the cornea, along the course of the path of the injection needle, caused practically no reaction.

Lens.—In 1939 the vapors of a substance which has been widely employed in the same manner as naphthalene to protect various materials from moths was held to be the cause of cataract in two patients. The substance held responsible was paradichlorobenzene. Ever since the initial accusation

this substance has been regarded with suspicion as a potential cataractogenic agent; yet no further condemnatory evidence has appeared. In fact, all subsequent attempts to cause cataract by administering paradichlorobenzene to animals have been unsuccessful. Recently, all the evidence has been thoroughly reviewed, additional animal experiments have been carried out, and workmen exposed to the material industrially for as long as 25 years have been examined ophthalmologically, but no indication of cataractogenic effect could be found except for that in the claim of 17 years ago.[58] Thus, serious doubt has been cast on the validity of the initial accusations, and it has been pointed out that the identity or purity of the material originally suspected of causing the cataracts was not well established.

A most interesting and practical question has been raised concerning whether miotic drugs might cause gradual development of cataracts.[98] This question arose as a consequence of an observation of development of striking clouding in the lenses of several middle-aged patients in the course of 6 to 18 months during treatment with various miotics for glaucoma. It was properly recognized that this could well be coincidental and that many patients use miotics for years without development of cataract; nevertheless, it seemed worth while to examine the effect of miotics on the lens experimentally. It was found that pilocarpine in vitro at 0.001 M concentration and Mintacol even at 10^{-6} M caused considerable inhibition of oxygen uptake by the lens. Furthermore, in rabbits which were treated topically with 2% pilocarpine for several days the respiration of the lenses was strongly inhibited, although no cataract was produced. It has not yet been determined whether in patients the miotic drugs reach sufficient concentration in the aqueous humor to interfere with respiration of the lens, nor has the significance of depressed utilization of oxygen been ascertained. The subject certainly merits further exploration.

The influence of a number of other drugs and poisons on various aspects of lens metabolism have been examined in vitro, but with no particularly noteworthy new findings; substances tested were dinitrophenol, edathamil, acetazolamide, phenylbutazone, cyanide, fluoride, and iodoacetate [51,68,69]

Induction of cataracts in rabbits by administering alloxan is now well known and has already been studied from many standpoints; recently, morphologic studies on the degenerating cells of the lens have shown the Golgi apparatus to disappear and the mitochondria to become deformed prior to the appearance of slight abnormalities of the ciliary body and iris.[69] Poisoning of rabbits by cobalt chloride has been observed to cause cataracts, associated with degenerative changes in the choroid, retina, and optic nerve.[3] The quantities of cobalt administered were sufficient to cause cirrhosis of the liver and hyperplasia of the spleen. No ocular effects have yet been reported in human beings, and the dosage of cobalt employed clinically in treatment of anemias is relatively small.

Visual disturbances which result from the miotic and cyclotonic actions of inhibitors of cholinesterase such as TEPP are very well known to ophthalmologists, who utilize substances of this sort in treatment of glaucoma. In application of TEPP agriculturally as an insecticide by spraying from airplanes, several fatal accidents have occurred when the pilots have become poisoned. A recent reinvestigation of the visual effects of TEPP has substantiated earlier observations on dimness and blurring of vision and has added the observation that unequal involvement of the two eyes may occasionally add to the difficulty in judging distances.[133]

Retina and Optic Nerve.—The conclusion has been reached and has apparently been generally accepted that retrolental fibroplasia of premature infants has been caused by the administration of oxygen. A recent extensive survey of the subject points out that

any concentration of oxygen in excess of that normally present in the air presents a risk of inducing retrolental fibroplasia in premature infants, and the risk of inducing retrolental fibroplasia in premature infants increases with the concentration and length of time of exposure. Contrary to impressions occasionally entertained previously, it appears that the rate of withdrawal from the oxygen-enriched atmosphere does not have an important influence in the pathogenesis of the disease.[66] Speculations on the possible enzymatic basis for oxygen toxicity to the retina have been offered by a leading biochemist, and these might well serve as a guide to further experimental work on the pathogenesis of retrolental fibroplasia.[10] However, with solution of the mystery of the cause of retrolental fibroplasia from the clinical standpoint, there appears to have been a decrease in the incentive to study the disease experimentally. In the year under review, experimental investigation has shown that oxygen-induced abnormalities of retinal function are detectable by means of electroretinography in rabbits.[48]

Two new and apparently highly selective intoxicants of the retina have been discovered, piperidylchlorophenothiazine and a series of diaminodiphenoxy alkanes. The toxicity of the chlorophenothiazine compound, known medically as N. P. 207, is of particular interest because this substance is closely related to the well-known drug chlorpromazine and has even more desirable actions on the central nervous system. Unlike chlorpromazine, which has not exhibited significant toxic effects to the eye, N. P. 207 has been found to cause retinal pigmentary degeneration in patients.[65,109,137,139] Individual susceptibility varied considerably, but at dosage levels required for the desired effect on the central nervous system roughly one- to two-thirds of the patients developed fundus abnormalities within one to three months. In several instances the abnormalities appeared after the drug had been discontinued. The earliest symptom was hemeralopia. Visual acuity was not affected in most instances, but in a few patients it was seriously impaired. The visual fields became moderately contracted, and scattered discrete patches of abnormal retinal pigmentation gradually developed, slightly resembling retinitis pigmentosa. After withdrawal of the drug there has generally been some improvement, but in at least four cases the vision has remained very poor even after five months.[65] All efforts to induce toxic effects in animal eyes with N. P. 207 so far have been negative, and it appears that this drug has a high specificity for the human retinal pigment epithelium.

The diaminodiphenoxy alkanes, in particular 1,5-bis(*p*-aminophenoxy)pentane, were discovered to affect the vision of monkeys, dogs, and cats when these drugs were administered for evaluation as potential schistosomicidal agents.[34] Vision was impaired within 24 hours of administration, and the pupils became dilated and did not react to light. The site of the toxic action was found to be in the retina. Retinal vessels became constricted and retinal pigmentary degeneration and proliferation developed in two to eight weeks. Histologically, the outer layers of the retina, including visual and pigment cells, were found to be extensively damaged but the inner layers of bipolar and ganglion cells were preserved.

Concerning toxic amblyopia from well-known causes, a variety of observations have been added to the literature. A group of patients acutely poisoned with methyl alcohol were so successfully treated by administration of alkalinizing agents and ethyl alcohol that no loss of vision occurred.[129] This adds weight to the recommendations which have been made for this treatment on the basis of previous clinical experiences and conforms with the results of experiments in monkeys in which ethyl alcohol was found to have significant protective effect against methyl alcohol.[40]

A single case report of temporary blindness due to quinine poisoning has been added to the vast literature on this subject.[72] A relatively rare instance of recurring total blindness from digitalis has been described, and it seems likely that this was an instance

of cerebral cortical blindness, because the pupillary reflex to light remained active.[39] One case of transient amblyopia with constricted fields has been described in a patient receiving both quinidine and digitalis; the condition improved after quinidine was discontinued, and this has been presented as possibly the first case of toxic amblyopia due to quinidine.[97]

Electroretinographic studies on patients confirmed previous reports that in siderosis from intraocular foreign bodies of iron the ERG may be greatly affected even when the visual acuity is nearly normal.[117] The electroretinographic, metabolic, and morphologic changes in the retina which may be induced by a variety of poisons in rabbits have been further analyzed, but no particularly noteworthy conclusions were reached.[8, 73,91]

Investigation of the cause of optic neuritis and atrophy occurring in patients under treatment with isoniazid (INH) and streptomycin for tuberculous meningitis has established that this complication occurs only when isoniazid is administered by intrathecal injection.[22,24]

Finally, a valuable comprehensive review of toxic amblyopia has been provided by Frank Carroll.[28]

Muscles.—Several cases of squint and papilledema have been described in children suffering from lead poisoning.[130] In this instance the lead came from burning lead batteries; most notoriously in the past it has come from eating lead paint. Children appear to be more prone to develop encephalitis with increased intracranial pressure, papilledema, and sixth nerve palsies as a result of lead poisoning than do adults. The most promising means now available for ridding the body of lead is the administration of edathamil calcium-disodium (calcium disodium ethylenediaminetetraacetate).

Administration of ethyl alcohol to human volunteers was found to induce nystagmus at a dosage of 50 ml. or more of absolute alcohol or its equivalent.[58]

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REFERENCES

1. Abrahamson, I. A., Jr., and Abrahamson, I. A., Sr.: Metimyd: A Clinical Study, Am. J. Ophth. 42:482-485, 1956.

2. Abrahamson, I. A., Jr., and Abrahamson, I. A., Sr.: Use of Iodo-Niacin for Retinal or Vitreous Hemorrhages and Vitreous Floaters, Am. J. Ophth. 42:770-772, 1956.

3. Alagna, G., and d'Aquino, S.: Ocular Changes from Cobalt Chloride, Arch. ottal. 60: 5-29, 1956.

4. Allen, J. H.; Manning, J. W., Jr.; Guidry, M. A., and Kelly, J. B.: Changes in Aqueous Flow and Blood-Aqueous Barrier After Hydrochloric Acid Burns to the Eye, A. M. A. Arch. Ophth. 57:1-6, 1957.

5. Apter, J. T.: The Effect of Hallucinogenic Drugs on the Electroretinogram, Am. J. Ophth. 41:1067, 1956.

6. Arentsen, J. S.: A Case of Acute Myopia with Glaucoma from Ingestion of Diamox, Arch. chilen. oftal. 13:82-84, 1956.

7. Babbott, E.: The Effect of Certain Drugs on Corneal Impedance, A. M. A. Arch. Ophth. 57:425-429, 1957.

8. Babel, J., and Ziv, B.: Researches on Experimental Retinal Degenerations: Histologic and Electroretinographic Studies, Ophthalmologica 132:65-75, 1956.

9. Back, M.: Transient Myopia After Use of Acetazoleamide (Diamox), A. M. A. Arch. Ophth. 55:546-547, 1956.

10. Barron, E. S. G.: On the Mechanism of Oxygen Poisoning, Am. J. Ophth. 41:1069, 1956.

11. Bauer, W., and Singh, M. M.: Management of Gout, New England J. Med. 256:171-176, 1957.

12. Becker, B., and Christensen, R. E.: Beta-Hypophamine (Vasopressin): Its Effect upon Intraocular Pressure and Aqueous Flow in Normal and Glaucomatous Eyes, A. M. A. Arch. Ophth. 56:1-8, 1956.

13. Bennett, G.: Cortisone Therapy of Visual Loss in Temporal Arteritis, Brit. J. Ophth. 40: 430-433, 1956.

14. Berggren, L.: On the Appearance of Fluorescent Dyes in the Aqueous Humor After Intravenous Injection, Am. J. Ophth. 42:595-601, 1956.

15. Bettman, J. W., and Fellows, V. G.: Factors Influencing the Blood Volume of the Choroid and Retina, Tr. Am. Acad. Ophth. 60:791-805, 1956.

16. Blackman, J. G.; Fastier, F. N.; Patel, C. M., and Wong, L. C. K.: Assessment of Depressor Activity and Mydriatic Activity of Hexamethonium Analogues, Brit. J. Pharmacol. 11:282-288, 1956.

17. Blodi, F. C.: The Effect of Some Newer Ganglionic Blocking Agents on Accommodation, Am. J. Ophth. 42:747-751, 1956.

18. Boberg-Ans, J.: On the Corneal Sensitivity, Acta ophth. 34:149-162, 1956.

19. Bock, J., and Stepanik, J.: Tonographic Investigation of the Effect of Depressin on the Eye, in Modern Problems in Ophthalmology, edited by E. B. Streiff and J. Babel, Basel, S. Karger AG., 1957, Vol. 1, pp. 115-120.

20. Boet, D. J.: Clinical Results with Phosphoryl Choline Calcium, Ophthalmologica 132: 150-152, 1956.

21. Bohringer, H. R.: On Local Therapy with New Cortisone Derivatives and Cortisone Combinations, Klin. Monatsbl. Augenh. 129:265-266, 1956.

22. Böke, W.: Investigation of the Question of Optic Nerve Injury During INH Treatment, Deutsche. Ophth. Gesellsch. 59:282-283, 1955.

23. Böke, W.: The Effect of Cortisone in Experimental Ocular Anaphylaxis, Ber. deutsche. ophth. Ges. 60:216-218, 1956.

24. Böke, W., and Janssen, G.: Experimental Investigations in Animals on the Question of Optic Nerve Injury by INH, von Graefes Arch. Ophth. 158:334-345, 1957.

25. Boros, B., and Takáts, I.: Comparative Investigations on Antihistaminics, Ophthalmologica 132:386-395, 1956.

26. Brooser, G.: Effect of ACTH on the Intraocular Pressure, Szemészet 93:75-79, 1956; abstracted, Zentralbl. ges. Ophth. 68:145, 1956.

27. Campbell, D. A.; Tonks, E. L., and Jones, M.: Correlation of the Systemic and Intraocular Effects of Diamox, Brit. J. Ophth. 40:283-294, 1956.

28. Carroll, F. D.: Toxic Amblyopia, Tr. Am. Acad. Ophth. 60:74-82, 1956.

29. Carpenter, C. P.; Pozzani, U. C.; Weil, C. S.; Nair, J. H., III; Keck, G. A., and Smyth, H. F., Jr.: The Toxicity of Butyl Cellosolve Solvent, A. M. A. Arch. Indust. Health. 14:114-130, 1956.

30. Christoferson, K. W., and Ogle, K. N.: The Effect of Homatropine on the Accommodation-Convergence Association, A. M. A. Arch. Ophth. 55:779-791, 1956.

31. Constant, M. A., and Becker, B.: Experimental Tonography. II. The Effects of Vasopressin, Chlorpromazine, and Phentolamine Methanesulfonate, A. M. A. Arch. Ophth. 56:19-25, 1956.

32. Constantinovits, M.: Treatment of Trachoma with Erythromycin, Klin. Monatsbl. Augenh. 129: 343-348, 1956.

33. Duke-Elder, S., and Goldsmith, A. J. B.: Cortisone and Corticotrophin in Ophthalmology, Practitioner 175:577-582, 1955.

34. Edge, N. D.; Mason, D. F. J.; Wien, R., and Ashton, N.: Pharmacological Effects of Certain Diaminodiphenoxy Alkanes, Nature, London 178:806-807, 1956.

35. Ellis, S.: The Metabolic Effects of Epinephrine and Related Amines, Pharmacol. Rev. 8: 485-562, 1956.

36. Fink, A. I., and Baras, I.: Effect of Steroids on Tensile Strength of Corneal Wounds, Am. J. Ophth. 42:759-764, 1956.

37. Fraser, H.: Oxyphenonium Bromide as a Mydriatic, Brit. J. Ophth. 40:751-753, 1956.

38. Friemann, W., and Overhoff, W.: Keratitis as Occupational Injury in the Oil-Herring Fishing Industry, Klin. Monatsbl. Augenh. 128:425-438, 1956.

39. Gelfand, M. L.: Total Blindness Due to Digitalis Toxicity, New England J. Med. 254:1181-1182, 1956.

40. Gilger, A. P.; Potts, A. M., and Farkas, I. S.: Studies on the Visual Toxicity of Methanol: IX. The Effect of Ethanol on Methanol Poisoning in the Rhesus Monkey, Am. J. Ophth. 42:244-251, 1956.

41. Gittler, R., and Pillat, B.: The Use of Decamethylene-Bis-(N-Methylcarbaminoyl-m-Tri-methylammoniumphenol) (BC 48) in Treatment of Glaucoma, von Graefes Arch. Ophth. 157: 473-494, 1956.

42. Gordon, D. M.: Prednisone and Prednisolone in Ocular Disease, Am. J. Ophth. 41:593-600, 1956.

43. Gramberg-Danielsen, B.: Megaphen in Ophthalmology, Klin. Monatsbl. Augenh. 129:252-254, 1956.

44. Grant, W. M., and Kern, H. L.: Cations and the Cornea: Toxicity of Metals to the Stroma, Am. J. Ophth. 42:167-181 (Oct., Pt. 2) 1956.

45. Grossmann, E. E., and Lehman, R. H.: Ophthalmic use of Tyzine: A Clinical Study of This New Vasoconstrictor, Am. J. Ophth. 42:121-123 (July) 1956.

46. Hagedoorn, W. G., and Maas, E. R.: The Effect of Histamine on the Rabbit's Cornea, Am. J. Ophth. 42:89-93 (July) 1956.

47. Hallett, J. W.; Wolkowicz, M. I., and Leopold, I. H.: Ophthalmic use of Neosporin, Am. J. Ophth. 41:850-853, 1956.

48. Hellström, B. E.: Experimental Approach to the Pathogenesis of Retrolental Fibroplasia: VII. Effect of Oxygen Exposure on the Electroretinogram in Kittens, A. M. A. Arch. Ophth. 55:211-219, 1956.

49. Herrmann, R. G., and Tust, R. H.: Studies on a New Cholinesterase Inhibitor, J. Pharmacol. & Exper. Therap. 117:75-81, 1956.

50. Hine, C. H.; Kodama, J. K.; Wellington, J. S.; Dunlap, M. K., and Anderson, H. H.: The Toxicology of Glycidol and Some Glycidyl Ethers, A. M. A. Arch. Indust. Health 14:250-264, 1956.

51. Hockwin, O.; Kleifeld, O., and Arens, P.: The Effect of Potassium Cyanide and Monoiodo-

acetic Acid on the Metabolism of the Lens, von Graefes Arch. Ophth. 158:47-53, 1956.

52. Hodgson, T. H., and Hennighausen, S.: Preliminary Studies on the Effect of Diamox on Ascorbic-Acid Levels in Aqueous Humor, Am. J. Ophth. 41:693, 1956.

53. Hoekenga, M. T.: Ocular Toxicity of Whipcide (3-Methyl-1-Pentyn-3-yl Acid Phthalate) in Humans, J. A. M. A. 161:1252-1253, 1956.

54. Hofmann, H.: On the Effect of Muscle Relaxing Agents on the Eye, Klin. Monatsbl. Augenh. 130:32-38, 1957.

55. Hofmann, H., and Lembeck, F.: Pharmacologic Investigations on Isolated Human Extraocular Muscles, von Graefes Arch. Ophth. 158: 277-279, 1956.

56. Hollingsworth, R. L.; Rowe, V. K.; Oyen, F.; Hoyle, H. R., and Spencer, H. C.: Toxicity of Paradichlorobenzene: Determinations on Experimental Animals and Human Subjects, A. M. A. Arch. Indust. Health. 14:138-147, 1956.

57. Hollwich, F., and Ulmer, E.: Testing of Mydriatics Rol-7683/15 and 16 on Individuals with Normal Eyes, Klin. Monatsbl. Augenh. 129:684-685, 1956.

58. Howells, D. E.: Nystagmus as a Physical Sign in Alcoholic Intoxication, Brit. M. J. 1:1405-1406, 1956.

59. Iwata, K.: Effect of Pentapyrrolidinium Bitartrate on Intraocular Tension of Primary Glaucoma, J. Clin. Ophth. (Tokyo) 9:311-317, 1955; abstracted, Zentralbl. ges. Ophth. 67:34, 1956.

60. Jacobson, J. H., and Basar, D.: The Effects of a New Drug, Nylidrin, upon the Electroretinogram, A. M. A. Arch. Ophth. 56:865-868, 1957.

61. Jaeger, W.: Corneal Injury by Butyl Alcohol, Klin. Monatsbl. Augenh. 129:116, 1956.

62. Janes, R. G., and Calkins, J. P.: Effect of Certain Drugs on the Iris Vessels: The Action of Isoflurophate and Homatropine on the Rat's Eye, A. M. A. Arch. Ophth. 57:414-417, 1957.

63. Karaki, S.: Changes in Cellular Structure of Ocular Tissues in the Alloxan Diabetic Rabbits, Acta soc. ophth. japon. 60:251-280, 1956; abstracted, Am. J. Ophth. 42:161 (July) 1956.

64. Keeney, A. H., and Zaki, H. A.: The Role of Trypsin in Experimentally Induced Hyphema, Am. J. Ophth. 43:275-278, 1957.

65. Kinross-Wright, V.: Clinical Trial of a New Phenothiazine Compound: N. P. 207, Psychiat. Res. Rep. 4:89-94, 1956.

66. Kinsey, V. E.: Retrolental Fibroplasia: Cooperative Study of Retrolental Fibroplasia and the Use of Oxygen, A. M. A. Arch. Ophth. 56: 481-529, 1956.

67. Kleberger, E.: Review of the Use of Cortisone and Hydrocortisone in Ocular Therapeutics, Klin. Monatsbl. Augenh. 129:349-358, 1956.

68. Kleifeld, O., and Hockwin, O.: The Effect of Dinitrophenol (DNP), Ethylene Diaminetetraacetic Acid, Diamox and Butazolidin on the Metabolism of the Lens, von Graefes Arch. Ophth. 158:54-63, 1956.

69. Kleifeld, O.; Hockwin, O., and Aybeck, N.: The Effect of Sodium Fluoride on the Metabolism of the Lens, von Graefes Arch. Ophth. 158: 39-46, 1956.

70. Kleinert, H.: Investigations of the Ocular Pressure-Lowering Action of Diamox, Deutsche ophth. Gesellsch. 59:138-143, 1955.

71. Kleinert, H.: Treatment of Glaucomatous Pressure Elevation with Pilocarpine-Effortil Salve, Klin. Monatsbl. Augenh. 128:401-410, 1956.

72. Koeppe, H. W.: Severe Quinine Poisoning with Temporary Blindness, Therap. Gegenw. 95: 148-149, 1956; abstracted, Ophth. Lit. 10:856, 1956.

73. Kornblueth, W., and Ben-Shlomo, E.: Glucose Utilization of the Retina: IV. Influence of Toxic Substances and Enzyme Inhibitors, A. M. A. Arch. Ophth. 55:813-817, 1956.

74. Kuchle, H. J.: Experimental Investigations of the Effect of Megaphen on the Eye, Deutsche ophth. Gesellsch. 59:178-182, 1955.

75. Kuchle, H. J.: On the Influence of Megaphen on Experimental Ocular Inflammation, Deutsche ophth. Gesellsch. 60:224-229, 1956.

76. Langham, M. E., and Lee, P. M.: Action of Diamox and Ammonium Chloride on Formation of Aqueous Humor, Brit. J. Ophth. 41:65-91, 1957.

77. Larson, P. S.; Finnegan, J. K., and Haag, H. B.: Observations on the Effect of Chemical Configuration on the Edema-Producing Potency of Acids, Aldehydes, Ketones and Alcohols, J. Pharmacol. & Exper. Therap. 116:119-122, 1956.

78. Leach, E. H.: Ocular Changes in Monkeys Fed with Sanguinarine and Other Substances, Tr. Ophth. Soc. U. Kingdom 75:425-430, 1955.

79. Lebensohn, J. E., and Monninger, R. H. G.: Topical Isopropylarterenol (Isuprel) as Adjuvant Therapy in Noncongestive Glaucoma, Am. J. Ophth. 43:412-416, 1957.

80. Leopold, I. H.: The Therapy of Collagen Diseases, A. M. A. Arch. Ophth. 56:577-586, 1956.

81. Leydhecker, W.; Dardenne, U., and Helferich, E.: Concerning the Combining of Miotics, Deutsche ophth. Gesellsch. 60:89-100, 1956.

82. Lieb, W.: Papaveraceous Alkaloids and Intraocular Pressure, Deutsche ophth. Gesellsch. 59: 143-145, 1955.

83. Lieb, W., and Pirch, H.: Comparison of the Effect of Parasympathomimetic Drugs, Klin. Monatsbl. Augenh. 128:593-604, 1956.

84. Lieb, W., and Scherf, H. J.: Papaveraceous Alkaloids and Intraocular Pressure, Klin. Monatsbl. Augenh. 128:686-705, 1956.

85. Lincoff, H. A.; Breinin, G. M., and DeVoe, G.: The Effect of Succinylcholine on the Extraocular Muscles, Am. J. Ophth. 43:440-444, 1957.

86. Lippmann, O.: Local Irritating Effect Caused by Topical Use of Steroids in the Eye, A. M. A. Arch. Ophth. 57:339-343, 1957.

87. Lipsius, E. L.: Use of Sodium Saccharine for Testing the Functioning of the Lacrimal Passages, Am. J. Ophth. 43:114-115, 1957.

88. Lloyd, J. P. F.: Argemone Oil and Sanguinarine Poisoning in Monkeys, Tr. Ophth. Soc. U. Kingdom 75:431-433, 1955.

89. Long, J. P.; Luduena, F. P.; Tullar, B. F., and Lands, A. M.: Stereochemical Factors Involved in Cholinolytic Activity, J. Pharmacol. & Exper. Therap. 117:29-38, 1956.

90. Massmann, W.: Toxicological Investigations on Dimethylformamide, Brit. J. Indust. Med. 13:51-54, 1956.

91. Matisisaka, T.: Histochemical Study of the Retina: Effect of Iodoacetic Acid on Glycogen and Nucleic Acid in the Inner Segment of the Visual Cells of the Retina, Ann. ocul. 188:1071-1075, 1955.

92. McReynolds, W. U.; Havener, W. H., and Henderson, J. W.: Hazards of the Use of Sympathomimetic Drugs in Ophthalmology, A. M. A. Arch. Ophth. 56:176-179, 1956.

93. Merté, H. J.: Diamox Action in Glaucoma, Deutsche ophth. Gesellsch. 59:134-137, 1955.

94. Meyer-Schwickerath, G.; Gruterick, E., and Niesel, P.: The Effect of Butazolidin on Experimental Inflammations of the Fundus, Klin. Monatsbl. Augenh. 129:358-364, 1956.

95. Miller, E. M.: Effect of Acetazoleamide on the Dark-Adaptation Function in Glaucoma, A. M. A. Arch. Ophth. 56:869-877, 1956.

96. Miller, J. M.; Parke, D. W.; Surmonte, J. A.; Ginsberg, M., and Ablondi, F. B.: The Use of the Antibacterial Drugs and Streptokinase: Administered Intramuscularly in Enucleation of the Eye, A. M. A. Arch. Ophth. 57:241-244, 1957.

97. Monninger, R., and Platt, D.: Toxic Amblyopia Due to Quinidine, Am. J. Ophth. 43: 107-108, 1957.

98. Muller, H. K.; Kleifeld, O.; Hockwin, O., and Dardenne, U.: The Influence of Pilocarpine and Mintacol on the Metabolism of the Lens, Deutsche ophth. Gesellsch. 60:115-120, 1956.

99. Nieminen, K. A.: Conclusions Concerning Local Digitalis Therapy of the Eye, Klin. Monatsbl. Augenh. 129:687-691, 1956.

100. von Nordheim, R. W.: Effect of Naphazoline on Eye Diseases, Ophthalmologica 132:327-332, 1956.

101. Owe-Larsson, A.: The Local Effect on the Eye of Noradrenalin, Acta ophth. 34:27-34, 1956.

102. Paul, S. D., and Leopold, I. H.: The Effect of Chlorpromazine (Thorazine) on Intraocular Pressure in Experimental Animals, Am. J. Ophth. 42:107-112, 1956.

103. Paul, S. D., and Leopold, I. H.: The Effect of Tranquilizing and Ganglion-Blocking Agents on the Eyes of Experimental Animals, Am. J. Ophth. 42:752-759, 1956.

104. Paul, S. D., and Leopold, I. H.: The Effect of Vasodilatating Drugs on Choroidal Circulation, Am. J. Ophth. 42:899-902, 1956.

105. Perkins, E. S.; Smith, C. H., and Schofield, P. B.: Treatment of Uveitis with Pyrimethamine (Daraprim), Brit. J. Ophth. 40:577-586, 1956.

106. Quiroz, C.; Boyes, T., and Sacks-Wilner, A.: N. F. 12: A New Topical Solution for External Eye Diseases, Am. J. Ophth. 41:1020-1024, 1956.

107. Ralph, F. T.: Sympocaine: A New Local Anesthetic, Am. J. Ophth. 42:637-638, 1956.

108. Raymond, L. F.: Neovascularization of the Cornea Due to Butazolidin Toxicity, Am. J. Ophth. 43:287-288, 1957.

109. Rintelen, F.; Hotz, G., and Wagner, P.: N. P. 207, Méd. et hyg., Geneva 14:426, 1956.

110. Roberts, W. H., and Wolter, J. R.: Ocular Chrysiasis, A. M. A. Arch. Ophth. 56:48-52, 1956.

111. Robson, J. M., and Didcock, K. A.: The Effect of Isoniazid in Experimental Corneal Tuberculosis, Brit. J. Pharmacol. 11:190-197, 1956.

112. de Roetth, A., Jr., and Schwartz, H.: Aqueous Humor Dynamics in Glaucoma: Effect of Ganglionic Blocking Agents and Thiopental Sodium (Pentothal) Anesthesia on Aqueous Humor Dynamics, A. M. A. Arch. Ophth. 55: 755-762, 1956.

113. Rome, S.: Heparin in Senile Macular Degeneration: Preliminary Report, A. M. A. Arch. Ophth. 57:190-198, 1957.

114. Rosen, D. A.: Aqueous Humor Flow: The Effects of a Ganglionic Blocking Drug, Pentolinium, on Certain Aspects of Aqueous Humor Dynamics, A. M. A. Arch. Ophth. 57:361-365, 1957.

115. Ruedemann, A. D., Jr., and Noell, W. K.: The Effect of Epinephrine upon the Rabbit Electroretinogram, A. M. A. Arch. Ophth. 56:100-108, 1956.

116. Schirmer, K. E., and Ormsby, H. L.: Experimental Studies with Acetazoleamide in Anaphylactic Iridocyclitis in Rabbits, Am. J. Ophth. 41:667-671, 1956.

117. Schmoeger, E.: Electroretinography in Siderosis and Chalkosis, Klin. Monatsbl. Augenh. 128:158-166, 1956.

118. Schumacher, H.: Experimental Studies on the Manner of Action of Eserine on the Eye, Ophthalmologica 131:173-178, 1956.

119. Sery, T. W.; Paul, S. D., and Leopold, I. H.: Novobiocin, a New Antibiotic: Ocular

Penetrance and Tolerance, A. M. A. Arch. Ophth. 57:100-108, 1957.

120. Shapiro, H.: Swelling and Dissolution of the Rabbit Cornea in Alkali, Am. J. Ophth. 42: 292-300 (Aug.) 1956.

121. Smith, C., and Perkins, E. S.: The Preliminary Results of the Treatment of Uveitis with Daraprim, Proc. Roy. Soc. Med. 49:24-26, 1956.

122. Spiegl, C. J.; Scott, J. K.; Steinhardt, H.; Leach, J. L., and Hodge, H. C.: Acute Inhalation Toxicity of Lithium Hydride, A. M. A. Arch. Indust. Health 14:468-470, 1956.

123. Staenglen, K.: On Problems of Retinal Vasodilation Treatment and Results of Animal Experiments, von Graefes Arch. Ophth. 157:559-591, 1956.

124. Stark, H.: On the Effect of Heparin in the Treatment of Vascular Occlusions of the Retinal Arterial System Caused by Atherosclerosis, Klin. Monatsbl. Augenh. 130:72-82, 1957.

125. Suie, T., and Taylor, F. W.: The Effect of Cortisone on Experimental Pseudomonas Corneal Ulcers, A. M. A. Arch. Ophth. 56:53-56, 1956.

126. Swan, K. C.: New Drugs and Techniques for Ocular Anesthesia, Tr. Am. Acad. Ophth. 60: 368-375, 1956.

127. Swarup, N., and Row, M. V. J.: The Response of Ocular Diseases to Irgapyrin, Ophthalmologica 131:423-432, 1956.

128. Takaoka, S.: Change in the Intraocular Pressure and K-Ion Concentration in Serum and Aqueous by Diamox and Adrenalin, Acta soc. ophth. japon. 60:323-251; 281-284, 1956; abstracted, Am. J. Ophth. 42:166 (July) 1956.

129. Tonning, D. J.; Brooks, D. W., and Harlow, C. M.: Acute Methanol Poisoning in 49 Naval Ratings, Canad. M. A. J. 74:20-27, 1956.

130. Travers, E.; Rendle-Short, J., and Harvey, C. C.: The Rotherham Lead-Poisoning Outbreak, Lancet 2:113-116, 1956.

131. Turner, L.: Results from Prednisolone Therapy in Primary Inflammatory Conditions and Postoperative Complications of the Eye, Am. J. Ophth. 43:30-36, 1957.

132. Underwood, L. C.: Fatal Bone Marrow Depression After Treatment with Acetazoleamide (Diamox), J. A. M. A. 161:1477-1478, 1956.

133. Upholt, W. M.; Quinby, G. E.; Batchelor, G. S., and Thompson, J. P.: Visual Effects Accompanying TEPP-Induced Miosis, A. M. A. Arch. Ophth. 56:128-134, 1956.

134. Urrets-Zavalia, A., Jr.: Removal of Calcific Corneal Deposits with EDTA, Arch. oftal. Buenos Aires 31:64-66, 1956; abstracted, Am. J. Ophth. 42:527, 1956.

135. Ustimenko, L. L.: Application of a New Soviet Miotic Preparation Tetraethylmonothiopyrophosphate (A_8) in Glaucoma, Vestnik oftal. 69:11-18, 1956; abstracted, Chem. Abstr. 50:9608h, 1956.

136. Vail, D.: Ocular Ochronosis, Am. J. Ophth. 41:712-713, 1956.

137. Verry, F.: Pigmentary Degeneration of the Retina Caused by Medication, Ophthalmologica 131:296-303, 1956.

138. Vysckocil, J.: An Experimental Study of the Pathogenesis of Silicotic Granuloma in the Anterior Eye Chamber in Rabbits and Changes in Its Development Induced by the Action of ACTH, Insulin, Combinations of Both and Salicylates, Brit. J. Indust. Med. 14:30-38, 1956.

139. Wagner, P.: Investigation of the Effect of Phenothiazine Derivatives on the Fundus of Animals, Klin. Monatsbl. Augenh. 129:772-781, 1956.

140. Weekers, R.; Watillon, M., and deRudder, M.: Experimental and Clinical Investigations into Resistance to Outflow of Aqueous Humor in Normal Subjects, Brit. J. Ophth. 40:225-233, 1956.

141. Weisser, C. W.; Westrick, M. L., and Schrenk, H. H.: Action of Detergents in White Mineral Oil Upon Rabbit Corneal Epithelium, A. M. A. Arch. Indust. Health 14:265-268, 1956.

142. Wethman, A.: On the Influence of Vasodilators on the Vessels of the Retina, Klin. Monatsbl. Augenh. 129:231-251, 1956.

143. Wolf, M. A.; Rowe, V. K.; McCollister, D. D.; Hollingsworth, R. L., and Oyen, F.: Toxicological Studies of Certain Alkylated Benzenes and Benzene: Experiments on Laboratory Animals, A. M. A. Arch. Indust. Health 14:387-397, 1956.

144. Wudka, E., and Leopold, I. H.: Experimental Studies of the Choroidal Vessels: I. Historical Survey; II. Methods and Material of Investigation; III. Anatomical Observations, A. M. A. Arch. Ophth. 55:605-632, 1956.

145. Wudka, E., and Leopold, I. H.: Experimental Studies of the Choroidal Vessels: IV. Pharmacologic Observations, A. M. A. Arch. Ophth. 55:857-880, 1956.

146. Zahn, K., and Simkova, M.: The Effect of l-Noradrenalin on the Retinal Circulation, Ophthalmologica 131:65-71, 1956.

147. Chemical Lie Detector, Chem. & Engin. News 35:140, 1957.

Correspondence

CERTIFICATE IN OPHTHALMIC SURGERY

To the Editor:—The creation of a Certificate of Ophthalmic Surgery by the American Board of Ophthalmology has been announced in the American Journal of Ophthalmology and in the A. M. A. Archives of Ophthalmology (March, 1957, page 476). The following are some thoughts concerning this announcement.

The proposal to create a certification in Ophthalmic Surgery contains several unfavorable aspects.

First, it will lower the prestige of the American Board of Ophthalmology.

Second, it will brand as surgically incompetent all ophthalmologists who fail to possess this certificate.

The requirements for certification in ophthalmic surgery will be extremely difficult to obtain in areas of smaller population. There are many specialists certified by the Board practicing today in areas in which neither the surgical volume nor the necessary certified colleagues are easily available. This, of necessity, may prevent them from obtaining certification and will indirectly and unjustly brand these men as incompetent ophthalmic surgeons. Newly certified physicians will not be able to practice in smaller communities if they desire certification in ophthalmic surgery. Young men desiring to practice ophthalmology in smaller communities, faced with the almost insurmountable task of acquiring the qualifications for certification, while at the same time bearing the label of a "noncertified" ophthalmic surgeon, may well decide that to become a specialist certified by the American Board of Ophthalmology is not worth the effort. Areas of small population will be deprived of the competent ophthalmology that could and should be available.

The establishment of a certificate of ophthalmic surgery will decrease the prestige of the American Board of Ophthalmology. It will create the impression that present and future certified specialists are incompetent in ophthalmic surgery until they have practiced their speciality for at least three years, performed a large volume of surgery, and then obtained certification. Building a surgical practice and acquiring the volume of surgery necessary for the requirements, under these conditions, is practically impossible in small communities.

It is important to remember that in small communities a physician soon becomes very well known—not only his qualifications but his surgical successes and failures as well. It is also to be remembered that most hospital appointments are based on the possession of Board certification. If having a certificate of the American Board of Ophthalmology is not to mean competency in Ophthalmic surgery, it is conceivable that major privileges to do ophthalmic surgery may not be granted, thus further decreasing the opportunity to acquire such certification. It is equally conceivable that, in attempts to acquire, as rapidly as possible, the necessary volume of surgical cases, ill-advised or unnecessary surgery may be encouraged.

It is not, to be sure, the intent of the Certificate of Ophthalmic Surgery to deprive presently certified specialists of the prestige of the American Board of Ophthalmology, but it will surely accomplish this, and a majority of these specialists will automatically become incompetent surgeons. In announcing the creation of the Certificate of Ophthalmic Surgery, the Board is, in fact, stating that the majority of present certified specialists are incompetent surgeons; for if the feeling was that only a small minority were incompetent the concept of surgical certification would not have been proposed.

If there has been improper examination for surgical competency, this should be corrected. However, the manner of correction should be such that certified specialists may still build practices in small communities, that such physicians will

not suddenly be considered incompetent surgeons, and that the prestige of the American Board of Ophthalmology will not be destroyed.

JAMES C. CANNIFF, M.D.,
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To the Editor:—There has been much discussion and considerable written about the additional certification in ophthalmic surgery. There seems to be too great a lack of agreement in this field to make one feel that the movement is fully understood and accepted by the ophthalmologists throughout the United States.

We are a democracy and are proud of our heritage in which everyone has the right to be heard. I believe that it was wise to poll all of the members who hold certification from the Board of Ophthalmology and determine whether or not they were in favor of the additional certification.

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Society Transactions

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

I. S. Tassman, M.D., Chairman

William E. Krewson, 3rd, M.D., Clerk

January 17, 1957

Mandibulofacial Dysostosis (Treacher Collins Syndrome) LEONARD APT, M.D. (by invitation).

Mandibulofacial dysostosis is a congenital deformity of the facial bones which has not been described often in the American literature. Although the key manifestations involve the eye region, the syndrome is little known to the ophthalmologist in this country. A total of 121 cases were found in 69 articles up to part of 1956; 16 cases described in eight papers were reported from the United States—only two reports were by American ophthalmologists. I have seen four patients with this entity in less than one year at the Wills Eye Hospital, and previously I encountered five cases while at a children's hospital. This experience suggests that the disease is commoner than one would surmise.

The major clinical manifestations in mandibulofacial dysostosis are the following:

1. Eye. The palpebral fissures slope downward laterally ("antimongoloid"); coloboma in the outer portion of the lower eyelids; deficiency of cilia in the medial half of the lower eyelids; occasionally absence of the puncta of the lower eyelids and abnormalities of the nasolacrimal channels.

2. Facial bones. Underdevelopment of the malar, maxillary, and mandibular bones; macrostomia; fistulae or clefts between the angles of the mouth and the ears.

3. Ears. Malformation of the external ear, auditory canal, and middle ear (incus and malleus).

The appearance of these patients with the fully developed syndrome is that of a fish or a bird. This is particularly unfortunate because most of the patients are of normal intelligence. Persons with the incomplete syndrome—those with no gross abnormalities of the lower face or ears, may go unrecognized.

The facial malformations have been explained by a failure of differentiation of the mesodermally derived tissue of the first visceral arch at about the seventh week of fetal life. The absence of the stapedial artery, a vessel which is associated with the first visceral arch, recently has been offered as an explanation for the maldevelopment.

Three points are to be stressed in the practical management of these patients:

1. Early detection and treatment of deafness to allow normal mental and social development of the child. Deafness is a common feature of this syndrome and may not be suspected if there is middle ear but no external ear abnormality.

2. Investigation of the inheritance pattern by careful family history and by radiographic examination of the facial bones. There may be roentgenographic evidence of underdevelopment of the facial bones in persons who have no gross facial abnormalities.

3. The necessity of good supervision and close cooperation between ophthalmologist and general plastic surgeon to obtain optimal cosmetic results. Complications due to congenital obstruction in the lacrimal drainage system are handled in the usual way by the ophthalmologist.

Comparative Studies Using Primacaine HCl and Other More Commonly Used Local Anesthetic Agents. H. G. SCHEIE, M.D., and NEIL S. WILLIAMS, M.D. (by invitation).

Further studies are reported attempting to find a local anesthetic of sufficient duration to avoid the period of immediate postoperative pain following ocular

surgery. Primacaine HCl was made available on an experimental basis in June, 1956 (Novocol Chemical Manufacturing Company, Inc., 2911 Atlantic Ave., Brooklyn 7). Studies reported in this paper show that it has a duration of approximately one hour longer than procaine HCl or lidocaine HCl. It is an excellent anesthetic agent, causes no local irritation, and seems nontoxic. It is being extensively used for dental surgery, where it is considered to be the anesthetic agent of choice by many. The ideal anesthetic solution for ophthalmologic surgery should, however, have a considerably longer action to prevent postoperative pain.

We also report further experience with retrobulbar anesthesia with use of a polyethylene tube retained in the muscle cone. It has proved to be effective in relieving postoperative pain and has been used with safety in more than 600 patients.

The Pupil—Theoretical and Practical Considerations. MICHAEL CURCIO, M.D. (by invitation).

In clinical practice the pupil of the eye as it varies from patient to patient (and in the same patient from time to time) in size, shape, or position produces characteristic subjective visual effects. By far the most important pupil characteristic is that of size. Practical observations, supported by theory, show that size changes have clinically significant effects upon retinal image brightness and depth of focus. The latter further influences accommodative demand for near, the age of onset of the presbyopic syndrome, and the tolerability of refractive errors, even in younger subjects. In addition, effects upon adaptation time, subjective appreciation of small opacities, and extent of visual fields were reviewed.

Special observations upon the results of anisocoria were discussed together with some original suggestions for its management.

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

Isadore Givner, M.D., President

Byron Smith, M.D., Secretary

NEW YORK SOCIETY FOR CLINICAL OPHTHALMOLOGY

Max Chamlin, M.D., President

Richard J. Bellucci, M.D., Secretary

Joint Meeting, Jan. 21, 1957

Alternating Jaw-Winking Phenomenon (Motion Picture). JOHN T. SIMONTON, M.D.

This case of alternating jaw-wink is presented for two reasons: 1. This condition is relatively infrequent. Beaumont reported the first case in 1898; the second case was reported in 1930 by Marin Amat. 2. In the examination of infants, particularly, I feel that the lids should be observed while the infant is sucking on a bottle; otherwise, it is possible to miss the jaw-wink phenomenon, especially if the mother is the type who is not particularly anxious to reveal any unusual movement of the eyes or lids.

The case presented tonight is a 10-year-old girl who was first seen at the Lenox Hill Clinic about one year ago. As you will see in the movies, when the jaw moves to the right the left lid goes up. When the jaw moves to the left, the right lid goes up. However, in the primary position cosmetic appearance, I feel, is not bad enough to warrant surgery.

The first scene on the films shows a lack of tilting back of the head, and there is no head turn or head tilt to either shoulder. This patient has been followed for over a year, and her condition remains about the same.

Summary: A case of alternating bilateral jaw-winking phenomenon is presented. It is emphasized that the examiner should specifically look for the phenomenon in a routine examination of every eye case by having infants suck on a bottle or by having older patients move their jaw from side to side.

Panel Discussion on Ocular Motility

Members of the Panel.—Dr. Harold W. Brown; Dr. Walter H. Fink (by invitation), Minneapolis; Dr. William E. Krewson (by invitation), Philadelphia; Dr. Abraham Schlossman. Dr. Isadore Givner, Chairman of the Section, presiding for the first part of the discussion, and Dr. Max Chamlin, President of the Society, for the second part.

DR. GIVNER: *Dr. Brown, will you discuss the indications for surgical procedures in the handling of an overactive inferior oblique (recession, myotomy, myectomy)?*

DR. BROWN: The indications for these several surgical procedures are not as definite as the wording of this subject indicates. The recession operation can be used in the surgical handling of all cases of inferior oblique overaction. There are surgeons who advocate the abandonment of the myotomy and the myectomy procedures. They point out that the advantages of the recession operation outweigh the advantages of the myotomy and the myectomy procedures. The advantages of the recession operation are twofold: first, the safety factor involved, and, second, the more accurate gradation of the results of the operation. The safety factors have to do with the avoidance of a complete postoperative paralysis, which can occur following a large myectomy, and the prevention of making the mistake of operating on the lateral or inferior rectus instead of the inferior oblique. The more accurate gradation is assured because of the measured recession of the muscle. With these advantages I am in complete agreement. However, my experience with the myotomy and the myectomy procedures has convinced me that these procedures should not be abandoned. The advantages of the myotomy and of the myectomy procedures are, first, that less dissection is required to accomplish these procedures; second, that a greater effect can be obtained by a large myectomy than by a marked recession of the muscle, and, third, which is very important, that the myotomy and myectomy procedures are the only lengthening types of operations which can be done at the origin of the inferior oblique.

The indications for these surgical procedures in the handling of an overactive inferior oblique will depend on the advantages that each procedure offers in any individual case. For example, in a case of bilateral overaction of the inferior oblique, especially if the overaction is asymmetrical, the more accurate gradation of the correction by a recession procedure is more important than the less extensive dissection that would be required by a myotomy or a myectomy procedure. Also in cases in which a surgical procedure on the homolateral lateral rectus muscle is indicated, as well as a lengthening procedure on the inferior oblique, the recession operation is definitely indicated. The myectomy procedure is preferable in cases where there is a marked unilateral overaction of the inferior oblique. A myotomy or a myectomy procedure is indicated in many cases where a previous surgical procedure has been done at the insertion of the inferior oblique. The myotomy operation can be used as an alternative procedure to a recession operation, in cases of moderate unilateral overaction of the inferior oblique.

DR. GIVNER: Are there any differences of opinion?

DR. FINK: In the main I agree. I should like to point out one or two things which may be worth while to supplement what Dr. Brown has said. Working at the origin, in my experience, is unpredictable. I explain that on the basis of the fusion between the inferior rectus and inferior oblique. In some instances we get a complete paralysis of the muscle following surgery at the origin, and in some instances we get no effect whatever; in other words, there is great variability in the result.

In doing a recession, one may weaken the muscle, but many times there is a posterior fascial extension, in which case, if it is not severed, the effect of the operation will be lessened. I think that many of our poor results are due to this fact. By severing this posterior sheath expansion we can regulate a recession very accurately.

I should like to point out one more thing: There is only 16 mm. of muscle between the inferior rectus and the inferior oblique insertion, and if you recess the inferior oblique more than 8 mm. you may weaken the muscle excessively and create a paralysis of the inferior oblique.

DR. KREWSON: I have nothing to add, except that I wonder how often we get an overcorrection, clinically, when operating for overaction of an inferior oblique. In my experience, I have found it rather difficult to obtain sufficient correction, if the overaction was very large.

DR. SCHLOSSMAN: I agree with Dr. Brown on the main points.

DR. GIVNER: *Dr. Fink, will you (a) briefly discuss anomalous development as a causative factor in vertical defects and (b) state what are the anatomic factors which determine the selection of operative techniques in oblique surgery?*

DR. FINK: Anomalous development as a causative factor in vertical muscle defects will be presented in two parts: (1) anomalous development related only to the vertical muscles and (2) anomalous development related to the associated fascia.

(1) *Anomalies Related to the Vertical Muscles.*—A. Absence of a Vertical Muscle: Absence of a vertical muscle is a rarity and is a negligible factor in evaluating the cause of the mechanical defect.

B. Accessory or Rudimentary Vertical Muscles: Such deviations from the normal formation may be considered a rarity.

C. Fibrosis: Fibrosis of the horizontal muscles is relatively common. Such fibrosis also occurs in the vertical muscles in varying degrees and may be associated with fibrosis of the horizontal muscles.

Such anomalous development is more common than the literature indicates. Because of the nature of the anatomy in the region of the vertical muscles, a wide exposure of the area at surgery is not possible and, as the result, the nature of the anomaly may be overlooked. It is especially difficult to evaluate the character of the tissues in defects of mild or moderate degree.

D. Anomalies of Muscle Insertion: Although variation in the insertion of the vertical muscles may be sufficient to cause a mechanical problem, our evidence as to its actual role is difficult to evaluate.

E. Anomalies in the Plane of Action: Examination of anatomic material shows that the oblique muscle planes do not exactly coincide. However, most observers consider that for practical purposes the muscle planes should be regarded as the same, making an angle of about 51 degrees with the visual line. Any mechanical difference in the plane of action is neutralized by the adjustment capacity of the central mechanism.

In higher degrees of variation, however, as found in some of the 22 specimens showing greatest variation, it is possible that such a condition may create a mechanical obstacle to binocularity and, when associated with other etiologic factors, may be sufficient to produce a deviation.

(2) *Fascial Anomalies Associated with the Vertical Mechanism.*—There is little positive information available concerning fascial anomalies of the vertical mechanism. Because fascial anomalies are obviously present in the horizontal field, it seems logical to expect their presence in the vertical field also. Because of the limited exposure of the vertical area for inspection at the time of surgery, in addition to the complex nature of the normal anatomy, it is possible that many of the fascial anomalies in this area are overlooked, especially those of minor degree.

Fascial Anomalies Associated with the Vertical Rectus Muscles: 1. Anomalies limited to the fascia of the vertical rectus muscles. There is some evidence which indicates that such anomalies occur. I have found variation in connection with the fascial sheath of the superior rectus which suggested to me the anomalous state as described by Johnson.

2. Associated anomalies of the fascia and the vertical rectus muscle. Both fascia and muscle are involved.

Fascial Anomalies Associated with the Superior Oblique Muscle: The first type of anomaly of the superior oblique insertion consists of abnormal thickening

and fusion of the fascia bulbi adjacent to the fanned-out tendon of the superior oblique. The condition appears to be especially related to the fascia bulbi and trabeculae which immediately surround the oblique tendon.

The second type of fascial anomaly encountered involves the fascial sheath of the superior oblique tendon medial to the superior rectus. In these cases the sheath of the superior oblique is thickened and more inelastic than normal.

Fascial Anomalies Associated with the Inferior Oblique: The first type relates to the fusion between the sheath of the lateral rectus and the sheath of the inferior oblique at the point where the inferior oblique comes in contact with the lateral rectus.

The second type of abnormal fascial development in this region relates to the posterior expansion of the sheath of the inferior oblique near its insertion and fusion with the sheath of the optic nerve. In this anomaly there is a thickened, inelastic development of the posterior expansion of inferior oblique sheath.

Anatomic Factors Which Determine the Selection of an Operative Technique in Oblique Muscle Surgery.—Superior Oblique Muscle: The oblique turns downward, outward, and backward at an angle of about 54 degrees and is inserted into the posterolateral aspect of the globe. The tendon of the superior oblique from the trochlea to the insertion is about 18 mm. (¾ in.) long. There are 8 mm. of tendon from the nasal edge of the superior rectus to the insertion. The tendon is slightly oval, being 2.0 to 3.0 mm. in diameter. Beneath the superior rectus it fans out into a very delicate fibroelastic structure.

The superior oblique line of insertion is variable. The average length of the insertion is about 11 mm., and the anterior tip of the insertion is less than 0.5 mm. anterior to the equator of the globe.

The tendon is avascular tissue and does not lend itself to surgery.

The fascial membranes covering the reflected tendon may be described by dividing the area into two parts, the part from the trochlea to the medial edge of the superior rectus and the part beneath the superior rectus.

The first part of the sheath of the reflected tendon of the superior oblique is an extension of various fascial membranes. They form a sheath 2 to 3 mm. thick about the tendon, so that the tendon and its sheath together are 5 to 6 mm. in diameter. In this space are countless tiny, hairlike trabecular strands. Because of these fibrillae, independent movement of the tendon in this region becomes negligible.

The second portion of the superior oblique tendon covering, which is beneath the superior rectus, has a less complicated arrangement, being covered by only the fascia bulbi.

The anatomy of the area suggests the following surgical procedures as most feasible.

A. Severing of the superior rectus tendon is not necessary.

B. Tenotomy of the superior oblique tendon adjacent to the medial edge of the superior rectus seems the logical procedure to weaken the action of the overacting muscle. It is important that the fascial sheath be minimally disturbed.

C. A tuck adjacent to the insertion seems anatomically sound to strengthen the action of the underacting muscle, and it should not exceed 8 mm.

Inferior Oblique Muscle: In its lateral passage of about 16 mm. from the lateral border of the inferior rectus, the muscle recedes 3 to 4 mm.

The insertion of the inferior oblique is 9.5 mm. long and can vary from 5 to 14 mm. in length. The anterior tip of the inferior oblique insertion is about 9.5 mm. posterior to the insertion of the lateral rectus muscle and 2.0 mm. above the level.

The anterior expansion of the fascial sheath fuses with the fascial sheath of the lateral rectus, and the posterior fascial expansion fuses with the sheath of the optic nerve sheath.

The surgeon should be able to visualize the area near the posterior tip of the insertion and be aware of the important structures in the vicinity (macula area, optic nerve, ciliary nerves, and ciliary vessels).

The anatomy of the area suggests the following surgical procedures as most feasible:

A. It is not necessary to sever the lateral rectus.

B. Surgery should be performed at the insertion of the inferior oblique, for the following reasons: 1. The approach is easier and the operation can be carried out with the structures under direct vision. 2. The effect of the operation can be more definitely regulated. Variable results may occur because of the variations in the degree of fusion at the point of crossing of the two muscles. 3. Surgery at the origin of the muscle may disrupt check action in both the inferior oblique and the inferior rectus muscle.

C. The recession is the most logical procedure from an anatomic standpoint to weaken an overacting inferior oblique.

D. Resection and advancement is the most logical procedure to increase the effect of an underacting inferior oblique.

DR. BROWN: I should like to ask Dr. Fink whether, in his experience, some of these minor changes in the fascia, which apparently restrict movement, are sequelae of paralysis or whether they are the cause of paralysis.

DR. FINK: It is difficult to answer that question. Let us take, for example, the superior oblique tendon. It is my impression that there is an abnormal state of the trabeculae in that region, with a wider contact and fusion of the tendon to the globe than would happen in a secondary change. That is to a great extent supposition.

DR. GIVNER: *Dr. Krewson, what is the role of the obliques in divergent strabismus? What are the A- and V- syndromes? What are the indications and procedures for their surgery?*

DR. KREWSON: One of the secondary actions of the oblique muscles is abduction, and the simultaneous and equal action of the two obliques will assist the lateral rectus in outward rotation of the eye. Overaction of an oblique muscle therefore can be a factor in the production of divergent strabismus, and it undoubtedly is an important element in those cases that show a variation in the horizontal deviation in elevation and depression of the eyes.

As I understand it, the A-syndrome is that clinical picture in which exotropia becomes greater as the eyes are depressed, while the V-syndrome applies to exotropia which increases as the eyes are elevated. I first became acquainted with these terms when discussing Jampolsky's paper at the last meeting of the Academy. He attributes the divergence of the visual axis in depression to overaction or contracture of one or both superior oblique muscles, and he reported a number of cases with exceptionally good results following myectomies of these muscles. In like manner, he ascribes increase in divergence in elevation to overaction of one or both inferior oblique muscles and showed good results in myectomies of one or both inferior obliques. Also, he feels that it is not impossible to have simultaneous overaction of both oblique muscles in the same eye although he admits that this is seemingly an unphysiological process. The results in Jampolsky's cases were exceptionally good, but I do not feel that I can accept his premise.

In general, it is my feeling that cases of exotropia which increases in downward depression are due most likely to paresis of one or both inferior recti, and resections of the inferior recti together with horizontal surgery have been my choice of treatment. Likewise, cases which showed greater exodeviation in elevation I have attributed to paresis of one or both superior recti, and I have applied similar surgery to these elevators.

I am certain that recessions of the obliques will decrease an exodeviation, but I would expect that some crippling defects might appear at a later date.

DR. SCHLOSSMAN: I have been loath to operate on vertical muscles in exotropia, for the simple reason that in most of these patients the squint is intermittent and usually the patient's cosmetic appearance is fairly good. In addition, many of these patients can perform skilled work. Before we consider surgery on vertical muscles for this condition, the difference in measurement

between elevation and depression should be very large, at least 30Δ or 40Δ.

DR. FINK: I have always felt that in these cases the recti are at fault in downward and upward gaze. I have had instances in which it seemed an obvious situation. In these cases, I shift the insertion of the rectus medially; that is, the rectus is moved medially half its width. It seemed to help the situation somewhat. I do not think that severing the obliques is advisable. It would seem to me a more logical procedure to shift the recti medially to counteract the overactive obliques. It is possible, however, that an abnormal insertion of the superior or inferior oblique may be the basic cause in the A- and V- syndromes. When we have a patient who, on looking up or down, has eyes widely diverged, I think we should do something about it if we can, and I think that the most conservative method is to shift the recti and increase their adducting power.

DR. BROWN: In divergence, in lowered gaze, where there is overaction of the superior oblique muscles and underaction of the inferior rectus muscles, I have resected one or both inferior rectus muscles, with good results.

DR. GIVNER: *Dr. Schlossman, do the amount and type of surgery, as estimated preoperatively, correlate with the end-result in horizontal strabismus?*

DR. SCHLOSSMAN: Because of differences in techniques, it is difficult to set down definite, uniform rules for each surgeon to follow and to expect similar results. There are certain striking differences in surgical results: 1. Equal amounts of surgical correction often give different results in different patients with the same type and amount of strabismus. 2. Different types and amounts of surgical correction may yield identical results in cases with similar measurements.

Three factors favor good surgical results: 1. The same amount of surgery usually yields greater correction in patients with a higher degree of strabismus than in patients with a lesser degree of squint. 2. If glasses correct at least one-half of the esotropia, any procedure which is reasonably correct for the esotropia will give excellent results. 3. In hereditary cases, information obtained from the end-result of surgery on one member of a family in which similar types of squint prevail is a safe guide in planning surgical correction on another member of the same family.

DR. FINK: There are two or three points which I think might be worth while to mention; first, in working on infants, their eyes are smaller, and one must do less resection or recession on an infant than on an adult, because what we do is more effective on small eyes. The secondary changes in the muscle are not so pronounced in a young child as later in life, and we get much more effect in doing surgery on them.

In dealing with nystagmus we can easily overcorrect if we do the customary amount of surgery on the eye, because the deviation is easily overcorrected.

I think it is important to mention, in considering this question, that a recession is much more controllable than resection; also, a combination of recession and resection is much more effective in producing a result than when these steps are done independently. In exotropia I aim to overcorrect, and in esotropia I try to undercorrect. I believe that it is wise to do muscle surgery in steps rather than try to do too much at one time.

DR. GIVNER: *Dr. Brown, will you discuss surgical procedures used when a patient has a combined vertical and horizontal imbalance?*

DR. BROWN: This is a very interesting and complex subject. The surgical procedures which are usually effective in correcting a horizontal deviation are more likely to result in an over- or undercorrection when a patient has a combined vertical and horizontal imbalance. To a less extent, the same is true with surgical procedures used to correct vertical imbalances. The combined anomalies are common and occur in approximately 40% of all patients with strabismus. The surgically significant percentage is much lower. At times it is easy to recognize and evaluate the surgically significant combined imbalances. However, in a great many cases this is impossible and one will be obliged to correct the more obvious

deviation first. The less-obvious deviation may be accentuated and require surgery, or it may be minimized and require no surgery.

The most frequent surgically significant combination that occurs in convergent strabismus is that of the overaction of one or both of the inferior oblique muscles. The influence that the horizontal has on the vertical in the correction of this type of combined imbalance is important. As Dr. Krewson has pointed out, the oblique muscles exert their maximum vertical action when the eye is in adduction. To correct surgically both a convergent deviation and an overaction of the obliques, allowance must be made for a less prominent vertical action of the oblique which will result from the correction of the convergent deviation. To correct surgically a combined convergent deviation and an overaction of the vertical rectus muscles, allowance must be made for a more prominent overaction of these muscles following the correction of the convergent deviation. This is true because the vertical rectus muscles exert their maximum vertical action when the eye is in abduction. The surgical correction of the combined divergent and vertical deviations will require just the opposite allowance to that which has just been outlined for the combined convergent and vertical deviations.

The influence that vertical deviations have on horizontal deviations is also important. Prominent overacting obliques accentuate divergence. The inferior obliques accentuate divergence in upward gaze and the superior obliques accentuate divergence in lowered gaze. Overacting vertical rectus muscles result in the opposite type of horizontal incomitancy in up-and-down gaze. If this incomitancy is marked, the vertical deviation should be corrected first.

In addition to evaluating the influence that these deviations have on each other, it is important to recall that horizontal deviations can be secondary to vertical deviations. Also, vertical deviations can be secondary to horizontal deviations. Under these conditions it is essential to correct the primary deviation first.

In conclusion, the success of a surgical correction of these combined deviations may depend on which deviation is corrected first. Two general rules may help in determining which deviation should be corrected first. 1. If the horizontal deviation is secondary to, or is accentuated by, the vertical, the vertical should be corrected first. 2. If the vertical deviation is secondary to, or is accentuated by, the horizontal, the horizontal should be corrected first.

DR. KREWSON: I agree with everything Dr. Brown has said. I should like to emphasize one thing which Dr. Fink emphasized in answer to a former question: It is better, when we have these multiple deviations, to operate on one muscle at a time, if necessary, than to do too much surgery at one sitting.

DR. SCHLOSSMAN: I agree with the other panel members.

DR. FINK: Scobee gave a rule that has been sometimes of help, and that is this: If the vertical deviation is less than half the horizontal, we do the horizontal first, and if the vertical deviation is half of or greater than the horizontal we do the vertical first. I take one component at a time in most instances, unless the deviation is unilateral and the eye has amblyopia.

DR. CHAMLIN: *Dr. Fink, what are the pitfalls in vertical muscle surgery?*

DR. FINK: Do not operate too soon after the injury to a muscle. Do not operate on a dissociate type of defect. Do not delay surgery when it is indicated. Do not do too much in one step. Do not traumatize the tissues needlessly.

The Vertical Recti.—Surgery on the vertical recti is less predictable with respect to result than is surgery on the horizontal recti. Avoid excessive recession or resection. More than a 3 mm. resection may cause ptosis. Recessing more than 4 mm. may involve the tendon of the superior oblique and limit its action because it becomes attached to the scar tissue resulting from the surgery.

The Superior Oblique.—One may err in severing only the fascial sheath instead of the tendon in doing a tenotomy. In doing a tenotomy do not tear the sheath; instead make only a small opening and cut only the tendon. The tendon should be cut adjacent to the medial rectus, because an excessive weakening may result if the tendon is cut too close to the trochlea.

Tenotomy calls for definite indications, and, if the operation is not indicated, can cause the patient to be visually crippled because of the resulting torsion.

Tucking the muscle should be done by approaching from the lateral side of the superior rectus. The tendon and its sheath near the insertion is tucked. Do not tuck more than 8 mm. of the tendon. One may not recognize the tendon and only the fascia may be tucked. Trauma should be reduced to a minimum.

Gelfilm is of value in lessening adhesions.

The Inferior Oblique.—Operation at the origin gives unpredictable results. More predictable results are obtained in cases of recession at the insertion. Myectomy or myotomy is not as predictable as the recession operation and cannot be undone. The recession operation has the advantage that if too much effect is obtained the muscle can be reoperated on. Do not do more than an 8 mm. recession, and keep it in the correct line of action. The lateral rectus does not need to be severed in working on the inferior oblique. Care should be taken in working at the insertion because of the danger of injury to the macula, ciliary vessels, and nerves. Cut the posterior fascial sheath of the inferior oblique in doing a recession. Limit the trauma to a minimum, because adhesions result and lessen the result. Gelfilm placed between the operated on inferior oblique and the lateral rectus will help prevent adhesions.

DR. BROWN: I have a great deal of respect for the superior rectus, but I fear the inferior rectus more than the superior rectus. I have seen cases in which a recession of the inferior rectus resulted in a marked overaction of the homolateral inferior oblique. These cases had been operated upon for a vertical deviation caused by an old paresis of the contralateral superior oblique. The recession of the inferior rectus, in these cases, resulted in the correction of the preoperative diplopia in the vertical motor field of the inferior rectus. The operation also resulted in diplopia in all other fields of gaze, owing to the overaction of the homolateral inferior oblique. I concluded that the recession of the inferior rectus, in these cases, either unmasked a preexisting overaction of the inferior oblique or resulted in a more effective line of traction of the inferior oblique. I should like to know whether or not Dr. Fink has had any such experience.

DR. FINK: I also have great respect for both vertical recti. I have found that sometimes one thinks one has done just the right amount of surgery and one gets a marked under- or overeffect.

DR. KREWSON: I am certain that too many muscles are operated on before a correct diagnosis has been made. If one is not sure of the diagnosis, I think one should do nothing. While this may be very obvious, I think it is a comment worth making.

DR. SCHLOSSMAN: I have a great deal of respect, as have the other members of this panel, for vertical muscle surgery, except perhaps for that on the inferior oblique. Here we should consider the type of result we can anticipate. If it is chiefly cosmetic, we should tailor our procedure toward this end. Perhaps it would be advisable to perform less surgery on vertical muscles, thus saving ourselves a great deal of grief.

DR. CHAMLIN: Do you anchor that Gelfilm with sutures?

DR. FINK: Supposing we use a tuck of the superior oblique as an example. I take a small piece of Gelfilm and place it between the superior rectus and the tuck. I do not have to anchor it. You have to put it in quickly, because it softens rapidly and you cannot control it.

In inferior oblique procedures, I place it between the lateral rectus and the new insertion of the inferior oblique. In one instance in which an inferior oblique recession had been done six months previously, I operated on the lateral rectus and found the Gelfilm still intact.

DR. CHAMLIN: *Dr. Krewson, will you discuss the vertical displacement of the horizontal recti for the purpose of correcting a combined vertical and horizontal deviation?*

DR. KREWSON: It was my hope that Dr. Brown might discuss this subject in his answer to Question 5, on combined vertical and horizontal imbalance. Personally, I have not used this method in attempting to overcome a vertical

disturbance at the time of operating on the horizontal muscles. The method does not seem very logical to me; for, if we have a vertical defect, one or more of the vertically-acting muscles is probably at fault and so direct attention should be given to these faulty muscles, rather than to muscles that do not act in the vertical plane.

I am sure that displacement of the horizontally-acting muscles will have a vertical effect on the globe, for, unfortunately, I have experienced such a post-operative result when I know that I have obtained misalignment in reattaching a lateral or medial rectus muscle.

It is my understanding from the literature that insertion of the lateral rectus at a point above the primary insertion invariably causes elevation of the anterior pole of the globe, while insertion of the lateral rectus at a point below the primary insertion invariably causes a lowering of the anterior pole, and the same is the case for the medial rectus. Until recently it was not certain as to exactly what the effect of this transplantation might be. Alvaro has reported that for each millimeter of vertical distance between the primary position and the new position after the transplant a correction of 1 degree is obtained. This is for concomitant strabismus, either convergent or divergent, a recession of one muscle and a resection of the opposing muscle being done simultaneously. The results are said to be good, with no postoperative cyclophoria. As I have said, I have had no personal experience with this procedure.

DR. BROWN: I have done this procedure several times. In some cases there were encouraging results, and in other cases there was no change whatsoever. Adhesions above and below the point where the muscle has been sutured to the globe may be the reason why these effects have been so variable. I gave up this procedure many years ago. The great majority of vertical deviations increase in an oblique field of gaze; therefore I prefer to operate on the vertical-acting muscles to correct vertical deviations.

DR. FINK: As you know, Bielschowsky used this procedure for inferior oblique overaction. Foster has made definite claims as to the effectiveness of it. I believe he said that in the displacement of the width of a tendon combined with a resection he got 7Δ and that if he advanced the tendon and displaced the muscle the width of the insertion he got 11Δ or 12Δ. I feel that it is dangerous to carry out this procedure because of the cyclodeviation one is likely to get.

DR. CHAMLIN: Dr. Krewson, do you suppose that spreading the tendon insertion with two sutures helps to avoid torsional deviations?

DR. KREWSON: I always use two sutures in a recession or a resection to spread out the muscle and to attach it firmly. I think that the method would be helpful in this case, but I do not practice the displacement of the horizontal recti to correct a vertical deviation.

DR. CHAMLIN: *Dr. Schlossman, will you discuss unilateral vs. bilateral surgery in strabismus?*

DR. SCHLOSSMAN: The chief argument in favor of bilateral, or so-called symmetrical, surgery is that the resultant ocular movements are comitant. However, the panel member has observed that many well-executed recession-resection procedures give similar cosmetic results. If the ophthalmic surgeons feels fairly certain that bilateral surgery will yield the desired result, it is the operation of choice. If there is any doubt, or if the squint is large, a recession and resection on one eye should be the primary procedure; if further surgery is indicated, operation on the fellow eye can be planned, based on the result of the initial surgery. In amblyopia, unilateral surgery is preferred.

Recession of only one medial rectus frequently yields little correction. In esotropia of small degree or in accommodative esotropia with abnormal accommodation-convergence ratio, it may be advisable to perform the recession on the fixing rather than on the deviating eye.

DR. FINK: Symmetrical surgery is especially important in children, because there is greater possibility of a functional result when comitancy is present.

DR. CHAMLIN: You say that the amount of deformity for distance being greater than for near is rather rare in esotropia?

DR. SCHLOSSMAN: I have said that the presence of a very remote near-point of convergence in esotropia is very rare.

DR. CHAMLIN: Do the other members of the panel feel the same way about it?

DR. BROWN: It is rare, but it does occur.

DR. CHAMLIN: *How would you prevent overcorrection following horizontal surgery, Dr. Brown? How would you manage such overcorrection?*

DR. BROWN: Overcorrection following horizontal surgery can be prevented in the great majority of cases. To accomplish this prevention factors in the preoperative analysis, which indicate that overcorrection may occur, must be evaluated in each case. Also, errors in surgical technique must be avoided.

A few of these factors in the preoperative analysis of comitant convergent and divergent deviations should be considered.

In comitant convergent deviations the factor of spontaneous reduction of the magnitude of convergent deviation in many young children, due to growth and refractive changes, may be mentioned. Overcorrection due to this factor can be prevented by surgically undercorrecting the esotropia in young children and by surgically correcting only the nonaccommodative element of the deviation. Cross-fixation is another factor to be considered in the prevention of overcorrection. In cross fixation the patient on looking to the right fixates with the left eye, and on looking to the left fixates with the right eye. Bilateral medial rectus recession should be done guardedly, and, if the deviation is not great, lateral rectus resection is a safer procedure. The magnitude of the deviation at distant fixation, as compared to near fixation, is another important factor to be considered. Occasionally the deviation is greater at distant than at near fixation. When this factor is prominent, overcorrection can be prevented by bilateral resection of the lateral rectus muscles or by a small recession and a larger resection procedure on one eye.

Overcorrection in divergent deviations is a rare complication following horizontal surgery. In divergent deviations an important factor to be considered has to do with the magnitude of the deviation at near fixation in intermittent exotropia. When the deviation at near is not over 6Δ the patient should not be operated upon. When the exophoria is 10Δ to 15Δ, lateral rectus recessions should be limited to 3 to 5 mm., to prevent overcorrection. There is a rather practical test that may help in evaluating the deviation at near fixation. By placing 2+ spheres in addition to the corrected refraction and stabilizing the accommodation by an appropriate fixation object, a small exophoria may increase as much as 20Δ.

The age of the patient is another factor to be taken into consideration in the prevention of overcorrection following horizontal surgery. The age factor should be considered along with the safety limits of the recession operation. In children under 3 years of age the safe limit of the recession operation on the medial rectus muscle is 3 mm. and that on the lateral rectus muscle is about 5 mm. In an adult, unless the case is an exceptional one, the safe limit of the recession on the medial rectus muscle is 5 mm. and that of the recession of the lateral rectus muscle is 7 mm.

Careful technique in the performance of the operation itself can prevent some overcorrections due to postoperative fibrosis and adhesions. Fibrosis caused by hemorrhage into the muscle can be prevented by making the conjunctival incision well posterior to the insertion of the muscle. In this region the fascial attachments are loose and the danger of cutting into the sheath or the muscle, or both, is less. Also, the complication of postoperative adhesions between the muscle and the globe can be prevented if care is taken in the operative procedure not to injure the posterior sheath of the muscle. Injury to the posterior sheath of the muscle may result in extensive adhesions between the muscle and the sclera. These adhesions can result in limitation of the action of the muscle.

The second part of the question is "How would you manage such overcorrection?" Management of such overcorrection following horizontal surgery will require surgical treatment in most cases. Surgical management will depend upon whether or not the overcorrection has resulted in a comitant or in an

incomitant deviation and upon the magnitude of the overcorrection. In comitant overcorrection, where there is no limitation of the rotation of the eyes, one or both of the recessed muscles will require corrective surgery. A resection in addition to reattachment of the muscle to its original insertion may be, and usually is, necessary. The magnitude of the overcorrection is important. If the magnitude of the deviation due to the overcorrection is equal to the original deviation, it will require more surgery to correct the overcorrection than it did to correct the original deviation.

Incomitant overcorrection, where there is a limitation of rotation into the field of action of the recessed muscle, necessitates waiting until the muscle is exposed at the operation before it is decided just what to do. If the limitation is found to be due to secondary fibrosis of the muscle, it will be necessary not only to replace the muscle to its original insertion but also to resect some of the muscle. If extensive adhesions between the muscle and the sclera are found, freeing of the adhesions and resuturing of the muscle to its original insertion are indicated. It is also important to start active rotation of the eye a few hours after the operation to prevent the adhesions from re-forming. Another good method of preventing these adhesions from re-forming is to place Gelfilm between the muscle and sclera. An incomitant overcorrection that is found, at operation, to be due to an excessive recession will usually require a replacement of the muscle to its original insertion.

The prevention of overcorrection following horizontal surgery involves other factors, and the management of such overcorrection includes other procedures than those mentioned.

DR. FINK: I think that one should do more surgery than one would ordinarily do in these cases. I should also like to stress the importance of doing it early, not to delay too long before one does this surgery. I think in some of these overcorrections a vertical defect may be a factor in producing the overeffect. I have had some experience of overcorrecting cases with nystagmus, and I now do less surgery.

DR. SCHLOSSMAN: I think that Dr. Brown has covered the subject very well. There is only one point on which I would take issue. He said that if the deviation for near in intermittent exotropia is less than 6△ he does not operate. There are occasional patients in whom exotropia for distance is very large, causing a rather bad cosmetic blemish. I think that this type of patient should have the benefit of bilateral lateral rectus surgery, even though the near deviation may be slight or even nonexistent. Dr. Brown has had a lot of experience, and perhaps after producing overcorrection in several patients I may change my mind.

DR. CHAMLIN: Dr. Brown, would you say something on this point?

DR. BROWN: In reference to Dr. Schlossman's comments, I still maintain that I would not operate on a patient who has an exophoria at near of not more than 6△ in whom I cannot bring out more exophoria with 2+ spheres. In cases in which the exophoria at near is slightly over 6△, I would limit the recession of the lateral rectus muscles to 3 to 4 mm.

DR. CHAMLIN: You mentioned 3 mm. as the maximum recession; do you often do less than 3 mm?

DR. BROWN: The maximum recession of 3 mm. of the medial rectus applies to children in the 2-year-old age group. If the patient is younger than 2 years, it is possible to do a 2.5 mm. recession, although I do not measure that accurately.

DR. CHAMLIN: *Dr. Fink, will you discuss the newer techniques in muscle surgery?*

DR. FINK: *Superior Oblique.*—1. For weakening the overaction of the superior oblique, the most satisfactory recently introduced technique, in my opinion, is the tenotomy as described by Berke. It is superior to the method in which the insertion of the inferior oblique is moved toward the trochlea, as advocated by some British surgeons.

2. Operations for strengthening the superior oblique muscle: The superior oblique muscle may be strengthened by advancement (Wheeler, 1935), resection (McGuire, 1948), or tucking. For shortening the superior oblique the most

satisfactory technique, in my experience, is the tuck of the tendon adjacent to its insertion. As compared with the resection of the tendon, it is more controlled, causes less trauma, can be undone in case of an overeffect, and the possibility of a complete paralysis is less than may occur in a resection if the muscle pulls loose from its new position.

Inferior Oblique.—1. The resection and advancement of the insertion of the inferior oblique as described by McLean seems to offer the greatest possibility of improving a defect resulting from an underacting inferior oblique. As in the case of underaction of the other extrinsic muscles, such an operation has limitations. It does not restore activity to the muscle, although it does place the eye in a more advantageous position. When used in conjunction with a weakening operation on its antagonist, it is helpful. It is superior to a resection, because the reinsertion of the cut tendon to the previous insertion is a difficult step and also there is a greater risk of injury of the foveal area.

2. To weaken an overacting inferior oblique, the recession operation is the most satisfactory, in my hands. The result is more predictable, an overeffect can be corrected more easily, and the technique is not complicated.

Vertical Recti.—For strengthening the vertical recti where the underaction is pronounced, resection and advancement produce a better effect than resection alone.

If trauma is minimized and the tendonous insertion is trimmed close to the globe, the muscle will not reattach to the old line of insertion, especially if the muscle sheath at this point is intact. A piece of Gelfilm can be inserted over the old insertion line. Ptosis may develop if the amount of surgery is excessive.

In paralysis of the superior rectus it has been suggested that a very useful action results by transplantation of a 5 mm. wide central strip of the active levator palpebrae into the tendon of the superior rectus.

In paralysis of the superior or inferior recti it is possible to improve the action of the muscle by transferring a portion of the lateral rectus muscle to the site of the vertical rectus, the other portion of the muscle being shifted above or below its original insertion, depending on which vertical rectus is affected.

Horizontal Recti.—The tendon transfer in lateral rectus underaction as described by Hummelsheim is well known.

Weiner described a method in which the paralyzed lateral rectus is split in two and each half is sutured to a vertical rectus. More abduction is claimed with this method.

Hill described a technique for underaction of the medial rectus which offers good possibilities. He advocates it in absence or paralysis of the medial rectus. The procedure consists of transferring the superior and inferior recti to the site of the medial rectus. The lateral rectus is recessed.

Although muscle transference is not new in muscle surgery, we have as the result of recent work a better concept of the mechanism involved which explains the effect of the operation.

Paralysis of the Third Nerve.—Transplanting the superior oblique to the insertion of the medial rectus has been done for some years. It has been suggested that additional effect is possible in these cases if some action is given to the superior and inferior recti by splitting the lateral rectus and attaching the upper half to the superior rectus and the lower half to the inferior rectus.

Symmetrical surgery has been stressed by Costenbader. His results indicated that postoperative comitance is more frequently present when binocular simultaneous symmetrical surgery has been performed.

One of the big problems in muscle surgery is the tendency for scar tissue and adhesions to form. This is especially likely in surgery of the vertical muscles.

The use of Gelfilm, in my experience, is helpful in reducing adhesions which may nullify or lessen the result. It is nonirritating and remains for several months. It is especially of value in vertical-muscle surgery.

DR. CHAMLIN: *Dr. Krewson, what are some of the immediate and late complications of muscle surgery, and how do you cope with them?*

DR. KREWSON: Anything can happen as a complication of muscle surgery, and if we do enough surgery sooner or later we are bound to meet with unfortunate problems. Fortunately, it can be said that in general complications of muscle surgery are not common.

Some complications met with at the time of surgery or at the first dressing might be enumerated, the treatment of these being well known and perfectly obvious. Among these are corneal abrasions and tearing of the conjunctiva and of the capsule. Tearing of the tendon sheath or of the muscle fibers can lead to troublesome hemorrhage, and complete hemostasis must be obtained before final closure. Sutures can pull out of the sclera or of muscle fibers and, of course, must be reattached. It is possible to rupture the sclera when inserting sutures, or detaching a muscle, and the rupture must be repaired with suturing and diathermy. The opening of a vortex vein, or one of its branches, is probably best handled by coagulation. In opening Tenon's capsule it is possible to obtain prolapse of orbital fat, and this must be remedied by excision of the fat and suture of the capsule. Adhesions between the recti, or between the lateral rectus and inferior oblique, especially, must be detected and severed by sharp dissection. Frank infection or suppurative tenonitis occasionally occurs, though rarely. This is generally due to faulty technique, but it can be due to contaminated gut sutures. In such instances, sutures must be removed and the resulting disturbance corrected subsequently. In closing the conjunctiva, it is possible for Tenon's capsule to prolapse, or for one to obtain inadequate closure as a result of a loose suture or from tearing of the conjunctiva itself. Resuturing is usually necessary, although the conjunctiva will generally close itself, but the healing will be prolonged.

Late complications can include development of adhesions with unexpected deviations, the reversion of an eye to the preoperative deviation, and such conditions as secondary divergence following surgery for convergence. All of these require additional surgery and are too involved to discuss in detail. Dr. Brown has already discussed the matter of overcorrection. The widening or the narrowing of a palpebral fissure, or actual development of ptosis following surgery on a superior rectus, generally requires appropriate operative correction. Excessive scar tissue with cystic or granulomatous development at the operative site can only be improved by excision and suture of the conjunctiva. Fortunately, postoperative diplopia is usually not of long duration and intractable diplopia is rarely encountered. I know of no satisfactory means of handling this later condition.

DR. BROWN: One complication which sometimes follows surgery on the horizontal rectus muscles is extensive adhesions above and below the muscle. These adhesions, at times, limit the action of the muscle. I wonder how Dr. Krewson accounts for this, other than by surgical trauma.

DR. KREWSON: I do not know how to explain adhesions (I wish I did), but some patients are more prone to the formation of adhesions than others. I suppose it is on the basis of trauma. The only thing we can do is to reoperate and resect the adhesions.

DR. CHAMLIN: *Dr. Schlossman, will you briefly evaluate orthoptic training in the treatment of strabismus?*

DR. SCHLOSSMAN: Orthoptic training has great value in the treatment of the following conditions: 1. Amblyopia. This should not be limited to occlusion, but the patient should be taught to maintain fixation with his amblyopic eye. 2. Accommodative strabismus. Here the patient should learn to dissociate accommodation from convergence, so that he can maintain clear vision and keep his eyes straight without the use of glasses. 3. Convergence insufficiency. In this condition the positive fusional amplitude, namely, convergence, should be improved. 4. Preoperative and postoperative treatment. If some fusion is present, training is valuable both before and after surgery in order to consolidate and maintain a good functional result. 5. Special instances. An example of this type is the patient with well-controlled accommodative strabismus who begins to develop myopia. 6. Heterophoria.

DR. FINK: Scobee made the statement that 50% of his cured patients did not have orthoptic training, whereas with those that did have it he got 80% cures.

DR. CHAMLIN: *Dr. Brown, will you describe the superior oblique tendon sheath syndrome and its treatment?*

DR. BROWN: The superior oblique tendon sheath syndrome is a congenital anomaly. A complete or near-complete paralysis of the inferior oblique, either unilateral or bilateral, with a coexisting short tendon sheath of the homolateral superior oblique, is always present. This syndrome has certain clinical characteristics by which it can be identified. There are six which can be mentioned. First, and most characteristic, there is a failure of elevation of the adducted eye above the midhorizontal plane when it is in full adduction. Second, there is a widening of the palpebral fissure on adduction. This is in contrast to the retraction syndrome, in which there is a narrowing of the palpebral fissure on adduction. Third, there is little or no overaction of the direct antagonists to the affected inferior oblique, that is, the homolateral superior oblique. In the majority of these cases, there is no measurable vertical deviation in the field of maximum vertical action of the homolateral superior oblique. Fourth, there is little or no involvement of the homolateral superior rectus. This is evident by a near-normal muscle balance when the eyes are in upper oblique gaze to the side of the involved eye. Fifth, there is, on monocular or conjugate rotation of the involved eye in upward gaze, a limitation of elevation that follows a straight line from the midposition at the inner canthus to near full elevation in straight-up gaze. Sixth, there is either divergence or no change of the horizontal position of the eyes in straight-up gaze. This is in contrast to acquired paralysis of the inferior oblique, in which there is usually an increase toward an exodeviation in upward gaze.

The superior oblique sheath syndrome can be verified by the traction test. This test is done by rotating the eye in the fully adducted position and, with forceps, passively elevating the eye in adduction. The traction test is positive when there is marked limitation of elevation, and characteristically, in these cases, the eye cannot be elevated with forceps to any greater degree than the patient can voluntarily elevate the eye. There are some atypical syndrome cases in which there is a paretic involvement of the homolateral superior rectus.

The treatment of the superior oblique sheath syndrome cases will depend upon the functional and cosmetic defects which are present. Surgical treatment is not indicated in these syndrome cases in which there is no abnormal head position and fusion is present in lower gaze. If there is a backward head tilt, usually combined with a tilt to one shoulder, and a marked widening of the palpebral fissure on adduction, the sheath of the superior oblique can be severed (sheathotomy). This will render the traction test negative, and the patient will be able to adduct the eye without the occurrence of a disfiguring widening of the palpebral fissure. Very little improvement in elevation will be obtained by this procedure. The inferior oblique can be tucked at the same operation at which the sheath is severed. In the cases where there is no fusion or no possibility of fusion, the sheath and tendon can be severed. Good elevation in adduction results when both the sheath and tendon are severed, but at the expense of depression in adduction. In the atypical cases in which the superior rectus is involved, an operation on both the superior rectus and the sheath of the superior oblique can be done. In some of these cases the stretching of the superior oblique in its sheath between two muscle hooks has relieved the restriction to forceps elevation. After this procedure, a resection of the superior rectus has given good results. If there is a marked overaction of the homolateral inferior rectus, a recession of the inferior rectus could be done at the same operation.

DR. FINK: A British physician named Nutt reported about two dozen operations on this type of case, in which he did a tenotomy of the superior oblique and an advancement of the inferior oblique. Are you familiar with that?

DR. BROWN: No.

DR. FINK: Have you used the electrode to determine whether or not the inferior oblique is really paralyzed?

DR. BROWN: I have a case on which I am going to work with Dr. Breinin and try this, although he doesn't know it yet. The patient is an adult who has a typical superior oblique tendon sheath syndrome.

DR. CHAMLIN: *Dr. Fink, will you discuss the check mechanism of the extraocular muscles? What is its importance in surgery?*

DR. FINK: Although our knowledge related to the check mechanism of the horizontal muscles is fairly well established, very little positive evidence is available as to the check mechanism associated with the vertical muscles. This is understandable when one considers the greater complexity in the anatomic arrangement of the vertical muscles as compared with the horizontal muscles.

The fascial structures which are chiefly responsible for check action of a vertical muscle are those directly associated with the vertical muscles. These may be divided into two groups: the fascia associated with the vertical muscles above the globe (superior rectus and superior oblique) and the fascia associated with the vertical muscles below the globe (inferior rectus and inferior oblique).

The fascial sheaths and their expansions associated with the superior rectus and superior oblique tendon are fused together to form a continuous structure extending from the midpoint of the outer orbital rim to the midpoint of the medial orbital rim. It may be likened to a transverse fascial band extending across the orbit and may be referred to as the superior transverse fascial expansion. It is anchored securely to the periosteum of the orbital wall and has a limited amount of mobility.

The fascial membranes associated with the inferior rectus and inferior oblique likewise form a transverse fascial band, which may be referred to as the inferior transverse fascial expansion and is commonly known as the ligament of Lockwood. This structure is made up of the fused fascial expansions of the fascial sheaths of the inferior oblique and the inferior rectus.

When the globe is rotated downward, the superior transverse expansion moves forward and the inferior fascial expansion moves backward to an equal degree. The movement of the transverse expansion is reversed when the globe is rotated upward.

There is a limit to the amount of movement of these structures. When a vertical muscle contracts, the two transverse expansions are put to an increasing degree of stretch in opposite direction. Eventually a point in the rotation of the globe is reached where the fascial expansions have reached the limit of their movement and further rotation of the globe in that direction is stopped.

Other factors of less importance, such as the fusion to the fascia bulbi, also act to check the movement of the eye.

1. Check mechanism of the superior rectus. Check action of the superior rectus therefore involves two major factors, namely, the fascial membranes associated with the superior rectus (superior transverse fascial expansion) and the fascial membranes associated with the inferior rectus (inferior transverse fascial expansion, or ligament of Lockwood).

2. Fascial check mechanism, of the superior oblique muscle: Two factors are chiefly responsible for its check action. A major factor in the check action on the superior oblique is the fascial structure associated with the superior oblique reflected tendon. Another major factor in producing check action of the superior oblique muscle is dependent upon the fascial arrangement of its homolateral antagonist, the inferior oblique.

3. Check mechanism of the inferior oblique muscle: As in the case of the superior oblique, a major factor in the check action of the inferior oblique involves the fascia which immediately surrounds it. Another important check action affecting the inferior oblique involves the fascial structures related to its homolateral antagonist, the superior oblique tendon.

4. Check mechanism of the inferior rectus: As in the other vertical muscles, the fascial structure associated with this muscle is the primary factor and, in association with its direct antagonist, assists in the check action.

In regard to the second question, the check mechanism is essential to coordinated ocular movement and the attaining of single binocular vision.

Surgery of a muscle profoundly affects the action of its check mechanism and determines the final effect of the operation.

1. Too liberal severing of the fascia related to the muscle being operated on may create an excessive weakening of the restraining influence of the check mechanism. Such a lessening of the check action permits an excessive movement of the eye in the opposite direction and incomitancy.

2. To merely recess a muscle without severing its fascial expansions greatly lessens the operative effect.

3. The check mechanism is an especially important consideration if an abnormal state of the muscle exists, such as a contracture as seen in long-standing cases of strabismus or in fibrosis of the muscle.

4. In muscle surgery do not needlessly mutilate the check mechanism. Cutting or disturbing check ligaments excessively results in a greater amount of scar tissue, leading to contracture.

5. Excessive trauma or hemorrhage may create excessive scar tissue involving the fascia, which will distort the action of the check mechanism.

6. The check mechanism is an important consideration in transferring a muscle as in the Hummelscheim operation. It is possible that the fascial sheaths which create the check action of the transferred muscle, which are not transferred with the muscle, remain in their original position and to a degree lessen the effect of the muscle transfer and continue to exert much of the original action of the muscle.

7. In the case of the superior oblique an important function in the check action is its relation to its fascial sheath. If this sheath is excessively disturbed it affects the action of the superior oblique, causing it to overact. An excessive contraction of this sheath may limit not only the movement of the superior oblique but also that of the inferior oblique.

8. The extensions of the membranous sheath covering the inferior oblique anterior to the sheath of the lateral rectus and posterior to the fascia surrounding the optic nerve are important. In doing a recession of the inferior oblique at its insertion, it is important to sever these fascial extensions.

DR. BROWN: I became interested in the check mechanism of the oblique muscles in the sheath syndrome cases. Duane described the anterior sheath of the superior oblique as the check ligament for the inferior oblique, and the posterior sheath that extends from the trochlea back to the muscle as the check ligament for the superior oblique. I have talked to Dr. Fink about this, and he at that time felt that these structures were not the main check mechanisms of these muscles.

DR. FINK: I think they are one of the causes, but I think there is more to it than that. I agree with him on the main concept.

DR. CHAMLIN: *Dr. Krewson, will you summarize the present-day concept of amblyopia and its relation to surgery? Then will you briefly discuss what criteria can be used to judge the amount and type of surgery needed to correct for cosmetic purposes the deviation of a blind divergent eye?*

DR. KREWSON: Amblyopia appears to be the consequence rather than the cause of strabismus. It is functional in nature and not due to an organic or anatomic defect. The seat of the disturbance is not known; it might be said, however, that possibly this is located in the retinal neurons, and it may be an extension of a disturbance of higher structures in the central nervous system. It is certain that in amblyopia there is an inhibition of the higher cortical function of pattern vision, with no impairment of the lower cortical function of light perception. The behavior of the amblyopic eye in dim light has been shown to be similar in some respects to that of the normal eye under dark adaptation. The significance of this and other observations is not yet clear.

With relation to surgery, it might be said that an amblyopic eye has a small scotoma. The amblyoptic eye fixes eccentrically, and there appears to be a direct relationship between the depth of the amblyopia and the degree of eccentricity. That is, the more profound the amblyopia the greater is the shift away from the center. Other things being equal, therefore, the deeper the amblyopia, the greater amount of surgical correction required and the greater the difficulty in maintaining postoperative alignment.

From a practical point of view, it is my feeling that if a child is seen in infancy, before amblyopia has developed, early surgery might be regarded as an adjunct in the prevention of development of amblyopia. On the other hand, once amblyopia has been established, unless reasonably good vision has been regained, correction obtained by surgery will not be maintained and the patient will revert back toward the preoperative deviation. If amblyopia is very deep, with no possibility of improvement, and fixation is eccentric, in all probability surgery might be postponed until after the age of 12 or 15 in order to prevent, if possible, secondary divergence.

To correct for cosmetic purposes the divergent deviation of a blind eye, I know of no fixed rule which can be followed. It has been my practice to recess the lateral rectus to the functional equator, that is, 3 or 4 mm. posterior to the anatomic equator of the globe. In addition, I do a wide resection of the medial rectus. If the forced duction test or clinical observation reveals contracture or overaction of an oblique, I have no hesitancy in detaching either the inferior or superior or both obliques. In this regard it might be mentioned that the inferior oblique has greater abducting power than does the superior oblique. If correction is insufficient after these procedures, and frequently this is the case, I have done a marginal myectomy on the already recessed lateral rectus and have performed resection again on the medial rectus. Additional surgery can be performed on the fixing eye, but, in these cases, patient resistence to surgery on the non-deviating eye is generally encountered. I think it is well to warn the patient that more than one operation probably will be necessary, and it is well never to promise him too much in the way of a perfect result. However, since a blind divergent eye is very unsightly, these patients are generally very grateful for a reasonable improvement, although we as surgeons may be somewhat disappointed with our results.

DR. CHAMLIN: *Dr. Schlossman, will you discuss abnormal retinal correspondence and its relation to eye muscle surgery?*

DR. SCHLOSSMAN: Abnormal retinal correspondence develops only if a certain amount of binocular cooperation exists in the presence of suppression of the deviating eye. The fovea of one eye and an extrafoveal element of the other eye develop a common visual direction, giving rise to anomalous retinal correspondence. Surgery is the chief form of treatment in this condition. The ophthalmologist should plan the amount of recession or resection without considering the presence of normal or abnormal correspondence. Surgery rarely converts a patient from abnormal to normal retinal correspondence.

NEW YORK ACADEMY OF MEDICINE, SECTION ON OPHTHALMOLOGY

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Embryological Development of the Angle of the Anterior Chamber. ABRAHAM L. KORNZWEIG, M.D.

When the lens sphere separates from its attachment to the surface ectoderm, a wave of mesodermal tissue from the surrounding paraxial mesoderm grows across the space between lens and surface ectoderm. This takes place at the 10 mm. stage. This mesodermal tissue is later divided by a space which appears in its substance at about the 17 mm. stage into an anterior avascular mesoderm and a posterior vascular mesoderm, which is later to form the pupillary portion of the tunica vasculosa lentis. This space widens so that the architecture of an anterior chamber is indicated by the 25 mm. stage, at which period a vestigial cornea is present and the angle is indicated, although the iris has not yet appeared. During the third month the ectodermal layers of the iris have developed from the margins of the optic cup and are then growing anteriorly towards the lens. The mesodermal tissue that fills the angle differentiates into stromal iris tissue and trabecular tissue. As the eye enlarges, the iris continues to grow forward

and the angle deepens. This deepening can be best illustrated by noting the relationship of the base of the angle to several fixed points, namely, Schlemm's canal, the scleral spur, and the major arterial circle of the iris. At the beginning, all these structures are behind the base of the angle. Later, these structures come to lie partly in front and partly behind the base of the angle of the anterior chamber, until the final form is fully achieved. Atrophy or separation of the mesoderm at the base of the angle is essential for the normal flow of the aqueous in the anterior chamber through the trabeculae into Schlemm's canal.

A series of Kodachrome slides are presented showing the different stages in the development of the angle of the anterior chamber from the 10 mm. stage up to term.

Anatomy of the Angle of the Anterior Chamber. GERALD B. KARA, M.D.

In reviewing the literature of the past 50 years one finds much confusion regarding the anatomic landmarks and histologic components of the angle of the anterior chamber. Perhaps this was due to technical difficulties, such as inadequate methods of preparation and staining of histologic specimens. Recent studies, using tangential sections, have added considerably to our knowledge of this vital ocular structure.

The angle of the anterior chamber may be said to include the trabeculum, the canal of Schlemm, and the collector channels. The trabecular meshwork is subdivided into its inner (uveal) and outer (corneoscleral) components.

The uveal meshwork, which contains no elastic fibers, extends from Schwalbe's ring, at the periphery of Descemet's membrane, ranges beneath the scleral spur, and extends onto the longitudinal fibers of the ciliary muscle. Inner extensions of the uveal meshwork pass around the chamber angle to their attachments at the anterior iris root. The one or two lamellae which make up this region of the trabeculum are comprised of thin beams arranged in a single plane, to form irregular lacunae, which may be trapezoidal or rhomboid-shaped. The beams are of a collagenous core, with an outer covering of endothelial cells, which have large flattened nuclei and prominent nucleoli.

The corneoscleral meshwork, on the other hand, is rich in elastic tissue, with its lamellae extending from Schwalbe's ring and deeper corneal layers to the anterior scleral spur. Smaller segments may course posteriorly to attach to meridional fibers of the ciliary muscle. These lamellae, about 8 to 14 in number, are densely intermeshed medially and more widely separated peripherally, i. e., near the ciliary body. The broad flat beams comprising this meshwork anastomose freely; the spaces thus formed are oval, with the long axis running equatorially, that is, parallel to the scleral spur. These openings are smaller and more uniform in appearance than their counterparts in the uveal meshwork. The collagenous and endothelial structure of the individual beams is similar to that in the uveal meshwork.

While some authors claim histologic variations in the trabeculum with age, others find little correlation between age and appearance.

A few words about the drainage system: By means of serial microscopic sections Theobald traced and reproduced the drainage system from the anterior chamber through the trabeculum and the canal of Schlemm. Draining the latter, she found, are four vascular plexuses: the conjunctival, episcleral, intrascleral, and deep scleral. The deep scleral plexus serves as the direct connection between the canal of Schlemm and the collector channels. While the four plexuses do not anastomose freely with each other, there are numerous anastomoses of vessels within the individual layers. The external collector channels drain into the deep intrascleral plexus, branches of which anastomose with the episcleral veins to form the clinical aqueous veins.

We are all familiar with Ashton's classical studies, using Neoprene casts, wherein he disproved Friedenwald's contention of the existence of afferent vessels to the canal of Schlemm. More recently, greater controversy and speculation have arisen regarding direct communications between the anterior chamber and Schlemm's canal—the so-called endothelial-lined "canals of Sondermann."

Flocks has stated flatly that these apertures are artifacts, since he was unable to demonstrate them in serial tangential sections. He suggests they may be mechanical ruptures in the single layer of endothelium separating the outermost lamellae of the corneoscleral meshwork and the inner wall of the canal of Schlemm. This tissue, with the resultant small openings, 1μ to 2μ in diameter, he has termed the "pore tissue." On the other hand, Ashton's studies have led him to accept Theobald's findings, which essentially confirmed the presence of Sondermann's canals. He suggests these openings may be in the form of tortuous pathways, "wandering irregularly and obliquely through the meshwork, like channels through a sponge." I have no doubt that in the near future studies incorporating detailed dissection techniques and differential staining will settle this controversy one way or another.

The above is a rather brief outline of known and some unknown facts concerning a relatively small but vital portion of the ocular apparatus. The angle of the anterior chamber remains an intriguing subject for further histologic research.

REFERENCES

1. Anderson, J.: Hydrophthalmia or Congenital Glaucoma, London, Cambridge University Press, 1939.

2. Ashton, N.; Brini, A., and Smith, R.: Anatomical Studies of the Trabecular Meshwork of the Normal Human Eye, Brit. J. Ophth. 40:257-282, 1956.

3. Flocks, M.: The Anatomy of the Trabecular Meshwork as Seen in Tangential Section, A. M. A. Arch. Ophth. 56:708-718, 1956.

4. François, J.; Neetens, A., and Collette, J. M.: Mircroradiographic Study of the Inner Wall of Schlemm's Canal, Am. J. Ophth. 40:491-500, 1955.

5. Friedenwald, J. S.: Circulation of the Aqueous: V. Mechanism of Schlemm's Canal, Arch. Ophth. 16:65-77, 1936.

6. Sondermann, R.: Beitrag zur Frage der Resorptionswege aus der Vorderkammer, Ber. Versamml. deutsch. ophth. Gesellsch. 48:172-181, 1930.

7. Theobald, G.: Further Studies on the Canal of Schlemm: Its Anastomoses and Anatomic Relations, Am. J. Ophth. 39:65-89, 1955.

A Study of the Innervation of the Chamber Angle. MONTE G. HOLLAND, M.D.; LUDWIG VON SALLMANN, M.D., AND ELEANOR M. COLLINS, Bethesda, Md.

The innervation in the region of the chamber angle was studied in four classes of vertebrate eyes. The use of several silver-impregnation techniques, with serial sections on frozen and paraffin-embedded material, together with whole mounts of the anterior segment stained vitally with methylene blue, permitted a detailed examination of the origin, course, and termination of nerve fibers in this region.

The innervation was shown to consist of a plexiform arrangement of delicate preterminal and terminal axons which were interwoven in different planes and ended as free axonal filaments.

Axons terminating in this region originated from two systems of nerve fibers, the iridociliary plexus and the nerves which supply the cornea.

Free nerve endings were shown beneath the endothelium of Schlemm's canal and within the trabecular meshwork that forms the inner wall of Schlemm's canal.

In the human, monkey, rabbit, and chicken eyes no encapsulated or specialized nerve endings were observed in the area of the angle. In the chicken eye free nerve terminals were demonstrated in the adventitial wall of the sinus venosus sclerae.

The histologic observations are discussed on the basis of the current concept of the relation of nerve endings to their function, and attention is directed to the possible role of nerve fibers and endings in the regulation of intraocular pressure.

Tumors of the Angle. ALGERNON B. REESE, M.D.

Practically speaking, primary tumors of the angle do not exist. The angle, though, is implicated secondarily by tumors which fall into four categories:

1. Localized iris melanoma. When the question of local excision versus enucleation arises, the status of the angle in regard to tumor seeds is important, and also whether or not the tumor extends as far as or into the ciliary body. This latter point can sometimes be determined only by direct inspection. The presence in the angle of pigment dust in contrast to tumor seeds is no contraindication to local excision.

2. Ring melanoma. This is the nearest approach to a primary tumor in the angle, as this lesion spreads in the region of the major arterial circle at the junction of the iris and ciliary body.

3. Diffuse melanoma. This manifests itself first as an increased pigmentation of the iris in contrast to the fellow iris. Glaucoma is an early sign, and frequently it is considered to be secondary to an iridocyclitis. With the gonioscope, the presence of desquamated tumor cells in the angle is decisive.

4. Melanoma primarily in the ciliary body with extension secondarily through the root of the iris to the angle.

Lesions which may simulate tumors of the angle are the following: (*a*) intraepithelial cyst, (*b*) abortive or partial melanosis oculi whereby a quadrant of the iris shows the increased pigmentation—in such cases there are pigmented iris processes in the angle, (*c*) an encapsulated foreign body in the angle, (*d*) a granuloma from tuberculosis or sarcoid, (*e*) a sheet of desquamated pigment epithelium from the pupillary zone of the iris.

The Angle in Glaucoma Surgery. WILLIS S. KNIGHTON, M.D.

The important functional portion of the angle wall is the trabecular band sandwiched between the scleral spur and the ring of Schwalbe where Descemet's membrane ends. If this area is not readily accessible, or if it is not functioning properly, the aqueous humor is dammed back and the intraocular pressure rises. Operation must therefore be directed at freeing the angle, in the first instance, and providing a better outflow, in the second.

Closed-angle glaucoma and congenital glaucoma are the only two types of primary glaucoma in which the trabecular system is functioning normally but is blocked mechanically.

In closed-angle glaucoma, the trabecular drainage pathways must be blocked by iris before there is an increase in tension. As soon as they are unblocked, the tension drops back to normal and tonography shows no resistance to outflow.

Since blocking of the angle usually occurs as the result of higher pressure in the posterior chamber pushing the iris forward, the best insurance against renewed attacks is an operation to establish free communication between the two chambers so that the pressure will remain equal on the two sides of the iris diaphragm. Even a small peripheral iridectomy will suffice, and it leaves the angle itself unaltered physically and physiologically.

In some congenital glaucomas the trabecular zone is again embarrassed mechanically, this time by the presence of embryonic tissue. When this is scraped away, by Barkan's method, it leaves an intact, free, and normally functioning angle.

Secondary glaucomas may also be blocked by extraneous matter, lens, blood, exudate, etc. If this can be removed before organic changes take place, the angle is again restored to normal.

Chronic simple glaucoma is another story. Here tonography shows a resistance to outflow (even with an open angle), indicating an obstruction in the outflow channels, somewhere between the trabecular zone and the episcleral recipient vessels.

The operations to improve the outflow are therefore fistulizing, to establish external drainage of aqueous from the anterior chamber to the subconjunctival or suprachoroidal space. In all of these operations the anatomy of the angle is changed.

Goniopuncture makes a new fistulizing tract through the trabecular region to the outside subconjunctival area. The angle itself suffers little from the trauma, and the operation can be repeated.

Iridencleisis requires extreme care in preparing the angle recess for drainage and in manipulating the iris tongue for inclusion. Only in this way can deformation of the angle be held to a minimum. Even the best of care sometimes cannot avoid peripheral anterior synechias with further angle dysfunction. Each successive operation adds its own local adhesions, limiting the number of possible operations and adding to angle distortion.

Trephination likewise requires respectful attention to minimize trauma. Even so, unavoidable complications may leave the angle too distorted for subsequent effective surgery.

Cyclodialysis deliberately distorts the angle by making a visible open cleft. Fortunately, the attendant trauma need not be great, and the operation is often repeatable with fair expectancy of success.

Some of these operations distort the angle more than others; all of them have their share of success, but all of them are liable to complications which may render the angle less than useful.

The Management of Traumatic Lesions and Foreign Bodies of the Anterior Chamber Angle. HARVEY E. THORPE, M.D., Pittsburgh.

The author reported his personal experience with cases of injury and foreign bodies of the anterior chamber angle.

Gonioscopy is invaluable in recognizing small, occult hemorrhages, exudates, small iridodialyses, peripheral iridoschises, cyclodialyses, and minute foreign bodies lodged in the angle of the anterior chamber. In former years the Koeppe gonioscopic contact lens and the Troncoso goniolens were employed by the writer. In recent years the Goldmann mirror contact lens and more recently the Allen-Thorpe four-mirror gonioprism have largely supplanted the Koeppe lens for use with the slit-lamp biomicroscope. In freshly perforated cases one may use the Lister gonioscopic contact lens or the loose four-mirror Allen-Thorpe gonioprism for anterior chamber angle examination.

Methods of diagnosis and medical and surgical treatment of blunt injuries, penetrating wounds, and foreign bodies of the angle were discussed in considerable detail by the speaker.

Discussion

DR. BRITTAIN F. PAYNE: I feel particularly honored in being asked to present in five minutes a discussion of a monograph, a textbook, and a complete encyclopedia on foreign bodies. I was particularly impressed by the presentation of Dr. Kornzweig. For many years he has been interested in the development of the human eye. He has many beautiful specimens to demonstrate this development, and his sections, I think, show one thing conclusively: The angle of the iris does not develop until about the sixth or seventh month in utero. The iris at the 60 or 65 mm. stage (three months) is barely perceptible. There is no sign of Schlemm's canal. There is, it is true, the mesoderm, of which Dr. Kornzweig speaks, in the iris angle. The anterior chamber by that time is fairly well defined, if you use your imagination. It is not a true anterior chamber until there is developed the real iris angle with the corneoscleral trabeculae and the drainage channel, the canal of Schlemm.

In the interpretation Dr. Kornzweig has given us this evening he has discussed so much that there is really very little that I can add, other than to give a picture of the iris angle at the time of birth. This section represents the stage in which all of us have a great interest but which we have neglected. We have not studied the iris angle from the time of birth up to the first year of life to any great extent.

This specimen happens to be a section of a cyclops, for the specimen of which I am indebted to Dr. Boynton, of New York. It shows the iris angle to be about

normal for birth. The iris is not fully developed, and the iris angle is not well rounded out.

This next specimen represents a case of retrolental fibroplasia a few months after birth, and it shows an undeveloped iris angle. However, in the presence of retrolental fibroplasia a normal iris angle would not be expected.

I wish to congratulate Dr. Thorpe on his presentation here tonight. His encyclopedic knowledge of this subject of foreign bodies has given to us an appreciation of a great experience in this field. I do not know of anyone who has written or done more in this field than Dr. Thorpe. I, for one, was particularly impressed in talking to him tonight to learn that he was here as a student of the late Dr. George Dixon many years ago and actually made the diagrams of the apparatus and materials from the engineering standpoint, which had to do with the localization of foreign bodies. It has been a great experience for me to have seen so many excellent pictures shown here this evening. I am sure the members and guests feel the same way.

We, in New York, at least up to recent times, have not been as fortunate in our care of foreign bodies as Dr. Thorpe. I project this slide to show a penetrating wound with the remains of a foreign body lying in the anterior vitreous, which evidently was not very sterile, and then, a consequent abscess with endophthalmitis followed by enucleation of the globe. It seems to me that whatever treatment—extraction, antibiotics, or sulfonamide drugs—is pursued, nothing will save such an infected eye. I do not believe that Dr. Thorpe means to leave the impression that antibiotics will always save infected eyes. If the foreign body really infects the interior of the globe with virulent organisms, the eye will be lost in most cases, and I should like to ask him if he will comment on this in his closing remarks.

I was particularly impressed with his repair of the iris angle after rupture. If I remember correctly, I assisted Dr. Key in his monumental operation, and I remember the torture which Dr. Key and the rest of us underwent in the repair of the iris in that region. Dr. Key was probably one of the cleverest intraocular operators we ever had in New York, and he did a beautiful job in this instance, and the final visual result was 20/20.

Dr. Thorpe showed us a better method of uniting torn irides to the internal sulcus.

I have two minutes in which to discuss somewhat the presentation by Dr. Reese. I feel very humble in doing so, because I am a former pupil of Dr. Reese, and what little I know is attributable to him, Dr. Samuels, Dr. Theobald, and others. Dr. Reese has presented a textbook description on tumors of the angle of the iris, in spite of his denial of their existence. There are some instances in which we have secondary tumors of the iris angle, especially metastatic lesions. One of these was first recognized and reported here at the Residents' Meeting last May by Dr. Robert Reardon, of Lenox Hill Hospital, New York. The lesion was first seen in the eye as an angle tumor, and this slide shows it. The neoplasm was primary in the liver, epithelial in origin, and the first view of this lesion was in the iris angle. However, after the child died, and an autopsy was performed, we found that it had extended all the way back to the optic nerve.

A melanotic tumor in the region of the angle of the iris, which is not one of the angle at all, but is a proliferation within the ciliary body with the iris eroded and pushed to one side, is presented. This further confirms the thesis of Dr. Reese. The section Dr. Reese showed, in which there was a questionable melanosis of the anterior surface of the iris, may have been due to the pressure exerted by the interepithelial cyst, which was connected posteriorly with the ciliary processes and the iris.

Another section of a tumor, although primary in the iris, shows involvement near the iris angle.

A clinical photograph is shown to illustrate a malignant melanoma which has caused an iridodialysis. This is almost the clinical picture of the microscopic slide which Dr. Reese showed.

DR. ADOLPH POSNER: First, I should like to congratulate Dr. Givner, our Chairman, for this excellent program, which presents in a well-rounded manner one phase of ophthalmology. We are becoming more and more specialized, and tonight we have limited ourselves to the angle. I have gone even a bit further in specialization, because when anyone asks me how I examine the lateral angle I say, "I just don't; as a rule I limit myself to the inferior angle."

I am very sorry that Dr. Knighton could not be here tonight. His beautifully written paper was excellently presented by Dr. Merriam. It demonstrates to me that the angle is getting to play less and less of a role in glaucoma surgery, while it has gained in importance in the diagnosis of glaucoma. In glaucoma surgery we are not actually concerned with the angle. In angle-closure glaucoma we are concerned with the entrance to the angle, often visible with the slit lamp without the gonioscope. We try to create a communication between the posterior and anterior chambers. In single glaucoma we assume that the angle is not functioning, and we try to circumvent the angle by creating a fistula, either external, as in iridencleisis, or internal, as in cyclodialysis. We no longer believe, as we did formerly, that an iridectomy must be basal in order to open the angle. We know today that the more surgery we perform on the angle the more scarring we get and the less patent that region will be; in doing iridectomies, we now try to make them as small and as atraumatic as possible.

I should like to comment on Dr. Knighton's reference to Chandler's concept of relative pupillary block as a cause of angle-closure glaucoma. Between the posterior and anterior chambers there exists a pressure difference, but it is very small and not enough to produce an iris bombé. If it were true that pupillary block is a factor in angle closure glaucoma, then a peripheral coloboma should be effective, no matter whether it is close to the angle or near the pupillary margin. We know, however—and Curran knew it in 1920—that a peripheral iridectomy, or iridotomy, fails if it does not include the most peripheral part of the iris, where angle closure takes place. Here is a case in point: [slide] This man had angle closure glaucoma, asymptomatic, with tension in the 40's. Two of his sisters had been operated on successfully for angle-closure glaucoma by the late Dr. Mark J. Schoenberg, many years ago. Right after the operation I instilled a drop of atropine, which I used to do occasionally but have not done since. The pupil dilated, and the tension rose. Within two days the tension was 46 mm. I examined him with the gonioscope, and found that a thick, fleshy iris root had been left intact and was blocking the angle. Usually the root of the iris is thin and strips right off. In this case it was thick and had to be cut, and I did not cut it far enough peripherally. I instilled isoflurophate, and as the tension was dropping the artist made this drawing. You can see that the angle is beginning to open at one point. The rest of the angle is still closed, and you can see that there is contact between the two walls of the angle. The second picture was made 24 hours later and shows the angle open after the tension had dropped to 20 mm. I still have to use pilocarpine in order to keep the iris away from the anterior wall of the angle. If pupillary block had been the cause of the glaucoma, then why should it matter that a peripheral piece of iris was left intact?

In regard to Dr. Kara's paper I should like to say that some very beautiful work on the anatomy of the angle was published by Maggiore in 1919 and by Salzmann even before that. Dr. Theobald's researches have added greatly to our knowledge of the histoanatomy of the drainage channels. In my institution, the Manhattan Eye, Ear and Throat Hospital, as you all know, Teng, who is now in London, together with Paton and Katzin, has done some excellent histologic studies on the anatomy of the drainage channels, not only in normal eyes but also in glaucoma. They have shown that in senile eyes as well as in glaucoma there is collagenous degeneration of the trabecular fibers, as well as Schlemm's canal and the collector channels.

In regard to Dr. Holland's paper all I can say is that I admire the beautiful work and the painstaking attention to details which it demonstrates. I should like to ask Dr. Holland what he thinks of the work of Vrabec in which he demonstrated the presence of tactile corpuscles in the trabecular meshwork. This

is very interesting to me, because it may explain how the intraocular pressure can be regulated through nerve fibers and how one eye can affect the other eye, which we know to be a clinical fact when we do tonographies.

In conclusion, I should like to call your attention to the gonioscopic appearance of the normal and glaucomatous angles and to point out that the structures of the angle can be very easily identified. To make the diagnosis of angle-closure glaucoma you must be able to recognize two landmarks: the line of Schwalbe and the scleral spur. Between these landmarks are the trabeculae. Only the posterior two-thirds of the trabeculae actually function as a drainge channel, because that is where the canal of Schlemm is situated. If the scleral spur is not visible you are not sure that you see the entire trabecular band. If only the anterior third of the trabeculae is visible, it is not inconsistent with the diagnosis of angle-closure glaucoma. This slide shows gonioscopically a wide angle, while in this slide you see how the angle looks when it is very narrow. This angle is open. In order to differentiate an open angle from a closed one, we must use a very narrow slit-lamp beam. The parallactic displacement between the focal line on the iris and the focal line on the anterior wall of the angle gives evidence that the angle is open.

Here [slide] is an even narrower angle in a glaucomatous eye. This angle, too, is open and the tension may be quite normal.

In this slide, which is very similar to the previous one, but in which there is no parallactic displacement, the angle is definitely closed. After an attack of angle-closure glaucoma subsides, part of the angle will be open and part may still remain closed, as you see here [slide]. This does not necessarily mean that the tension is abnormally elevated, because aqueous may still seep behind the synechiae and drain through the trabecular meshwork. Moreover, if half the circumference of the angle is open you may still have a normal tension.

To conclude, I want to show two pictures taken from a paper of Ernst Fuchs, published in 1884 in *von Graefes Archiv für Ophthalmologie*. The first is that of a normal angle, shown for comparison. The next picture shows the angle of a woman who died of pneumonia in 1879 and who seven years previously had had a successful iridectomy performed for acute glaucoma. You see how the ciliary body is turned anteriorly. Modern drawings of angle-closure glaucoma frequently show an atrophied ciliary body. Actually, the ciliary muscle is very well developed, especially in hyperopes, but it is rotated so that it faces forward, as you see here, instead of toward the pupil, as in the normal eye. As a result, the root of the iris lies almost in an anteroposterior plane. The iris then makes a sharp turn and proceeds in a frontal plane. The angle thus formed projects against a prominent line of Schwalbe (which is the end of Descemet's membrane). This is the zone where angle closure begins, and this is where you have to perform the iridectomy. If, instead, you cut out a piece of iris nearer to the pupil, the patient will continue to have glaucoma.

DR. MONTE G. HOLLAND: In regard to Dr. Posner's question about Dr. Vrabec's studies: He studied the angle of four vertebrate eyes, viz., the carp, deer, goose, and human. In the goose eye he found an Herbst corpuscle in the trabecular region which appears morphologically similar to a Pacinian corpuscle and is presumed to have the same function. It should be pointed out that, of the four vertebrate eyes examined, it was observed only in the goose and presumably only in a single eye. Vrabec has not published additional evidence for the presence of specialized sensory endings in this area.

The present study comprises a part of the search for receptors and effectors mediating possible central nervous influences on aqueous outflow and aqueous formation. In this work, no specialized "neural end-organs" were observed in the region of angle in the vertebrate eyes examined. It should be pointed out that serial sections and several silver impregnating techniques were used, as well as specialized neurohistologic methods such as methylene blue vital staining utilizing whole mounts of bisected eyes.

The results of this study show that the innervation of this region is represented by a plexiform arrangement of delicate preterminal and terminal axons which terminate as free axonal filaments. In the presentation it was mentioned

that the absence of specialized endings or neural "end-organs" does by no means preclude the possibility that neural influences are involved in regulating the outflow of aqueous humor. Current knowledge indicates that free nerve endings, in every respect similar to those described, are sufficient for this purpose, since they are known to mediate a variety of "modalities"; also, in well-known pressure receptor areas (e. g., carotid bodies, great veins, aortic arch, etc.) only free nerve endings are present in a plexiform arrangement similar to that of the trabecular innervation.

DR. HARVEY E. THORPE: I want to thank the discussers for their courtesy and for the many things I learned from their comments.

There was a question by Dr. Brittain Payne with reference to the control of infections: If certain organisms get in, how can we control them? The immediate management of intraocular infection is often rather empiric. One proceeds with antibacterial measures while awaiting the results of cultures and antibiotic bacterial sensitivity tests. It is important to consider all ocular penetrating wounds as potentially infected.

Penicillin has generally proven to be the best antibiotic for Gram-positive organisms. We administer penicillin parenterally, sulfadiazine orally, and also chloramphenicol as a broad-spectrum antibacterial. They should all be given in large dosage to be effective. One should not delay antibiotic treatment until the organism is isolated and the results of sensitivity tests become available. Cultures made from the conjunctival sac may be misleading in the sense that bacteria isolated from the conjunctiva are not necessarily indicative of the offending organism that may have entered the eyeball. On a number of occasions we have extracted intraocular foreign bodies and have found the offending particle to be surrounded by pus. Cultures from the purulent foreign-body jacket were often different from conjunctival microorganisms. It is therefore advisable to remove the intraocular foreign body soon after its entry into the globe. It is important to take the immediate prophylactic measure against infection as previously mentioned.

The worst cases of intraocular infection are those which occur on farms, to workers who repair farm implements in barn environments. It is advisable to administer tetanus and gas bacillus antitoxin in such injury cases, with due precautions against serum sensitivity.

Aqueous penicillin should also be administered subconjunctivally. My experience with penicillin injections into the vitreous has been disappointing. I have never seen it save the sight of an infected eye. Von Sallmann, experimenting with rabbits, estimated the safe maximum dosage for an intraocular injection of aqueous penicillin to be 1500 units. Chloramphenicol has been shown by Leopold and co-workers to enter the aqueous more readily than some other broad-spectrum antibiotics. It should be used in large dosage (2 to 3 gm. as the initial dose and 500 mg. every six hours thereafter). Foreign-protein therapy is also advisable, either in the form of 10 cc. intramuscular milk injection or intravenous administration of typhoid. Extreme care must be taken with intravenous typhoid. It may be lethal if not used carefully.

The prognosis is guarded for blunt injuries of the chamber angle associated with extensive hemorrhage or with damage to the retina or the crystalline. Prognosis is fairly good for cases of foreign bodies in the chamber angle. In the presence of severe inflammation conjunctival chemosis and hypopyon, the outlook is guarded to grave. In general, one must be guided in treatment and outlook by the extent of anatomic and functional damage, as well as the complications that may ensue.

News and Comment

GENERAL NEWS

Two New Departments for Sibley Hospital.—Dr. John M. Orem, president of Board of Trustees of Sibley Memorial Hospital, Washington, D. C., announced establishment of two new departments for the proposed new Sibley Hospital for which a $1,500,000 fund drive is now under way.

The two new units, not originally contemplated in building plans, are a Department of Ophthalmology, under Dr. William M. Hart, of Bethesda, Md., and a Department of Psychiatry, under Dr. Zigmond M. Lebensohn, of Washington.

Sibley Memorial Hospital, which will be a 350-bed hospital and has become an integral part of The American University, at Nebraska and Massachusetts Avenues, will design the entire seventh floor of its new building for the two projected units.

Dr. Hart said that his eye-treatment section will have 30 beds, plus a clinic for outpatients. The arrangement will make possible a training program for eye surgeons, he added.

Dr. Lebensohn's unit will have 28 beds, according to present plans. The practicing psychiatrist, a former Navy medical officer, said that he hopes to offer special treatment for adolescents' problems and pastoral training in psychiatry for local clergymen.

Dr. Hart, an associate professor at Georgetown University and consultant in ophthalmology at Walter Reed Army Institute of Research, lives in Springfield, Va., although most of his work is in Bethesda.

ANNOUNCEMENTS

Wayne University Postgraduate Course.—The Department of Ophthalmology of Wayne University College of Medicine will give nine months' training in basic ophthalmology beginning Sept. 9, 1957.

Six mornings a week are spent in lectures and laboratories. Each afternoon students are assigned to eye clinics of affiliated hospitals. A fundus clinic is held weekly; also, one on muscles.

Students are given 120 hours of training in physiologic optics, 122 hours in histology and pathology, 60 hours in biochemistry, 40 hours in neuroanatomy, and other subjects.

Tuition is $300. Brochures on the basic science course will be mailed upon request. For further information write to Dr. A. D. Ruedemann, Chairman, Department of Ophthalmology, 690 Mullett St., Detroit, 26.

Books

A. M. A. Scientific Exhibits 1956. Sponsored by Council on Scientific Assembly, American Medical Association. Price, $10.00. Pp. 411, with numerous illustrations. Grune and Stratton, Inc., 381 4th Ave., New York 16, 1956.

While the exhibits of the A. M. A. Annual Meeting form one of the most valuable features for the visitors to the meeting, it cannot be said that this volume in any way is a satisfactory substitute for a visit to the exhibit itself. It is understandable that exhibits present almost unsurmountable difficulties to publication in book form. There is absolutely no uniformity in the illustrations as they are provided to the publisher, and in their present form the printed reproductions are useless. Even the wording ranges from type which is entirely illegible, unless one uses a magnifying glass, to billboard-size type which almost jumps out of the book. Ironically enough, the worst example of this occurs in the section on the ophthalmological exhibits. Unless the material from these exhibits can be changed for future editions, it is hard to understand why anyone would invest in these volumes.

The Head and Neck in Roentgen Diagnosis. By Eugene P. Pendergrass, J. Parsons Schaeffer, and Philip J. Hodes. Price, $37.50. Pp. 1759, with illustrations. Charles C Thomas, Publisher, 301 E. Lawrence Ave., Springfield, Ill., 1956.

The second edition of this very valuable and authoritative text on the roentgenological diagnosis of pathological conditions affecting the head and neck has been considerably enlarged and brought up to date. The second edition appears in two volumes, with a changed format, and a complete index of the subject matter is printed in each of the two volumes.

The chapters on the lacrimal passageways and the eye and the orbit will be of great interest to ophthalmologists. Methods of localization of foreign bodies are given in detail. The use of oxygen injected into Tenon's capsule is described, and various methods for obtaining x-ray images of the anterior portion of the eyeball, free of superimposed bone, and of the detection of small intraocular glass fragments are given. Intraocular calcification and ossification are considered. Dermoids and epidermoids of the orbit, retinoblastoma, arteriovenous aneurysm, meningiomas of the optic foramen, and liposarcomas are all considered from the radiological point of view. The chapter on cerebral angiography is particularly valuable.

These two volumes should be in the library of every hospital having a well-run eye service.

The Labyrinth. By Joseph Fischer. Price, $6.00. Pp. 206, with 30 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1956.

The main portion of this book, dealing with functional testing of the labyrinth, will interest chiefly otolaryngologists, but every ophthalmologist should have a reasonable understanding of the physiology of the labyrinth and its derangements. The author's approach to his subject has been largely physiological, and the first 26 pages deal entirely with physiology. There are other sections of the book which relate directly to ophthalmological problems, such as end-position nystagmus, conjugate paresis, and conjugate deviations, convergence spasm, labyrinthine strabismus, and optokinetic nystagmus.

The Merck Manual. Edited by Charles E. Lyght. Ninth edition. Price, $6.75. Pp. 1870. Merck & Co., Inc., Rahway, N. J., 1956.

This little manual of 1870 finely printed pages on good India paper fulfills many needs for the busy physician. The section on the eye is over 50 pages, and contains a condensed account of most of the commoner conditions which the

general physician will be called on to treat. The material has been kept up to date—glaucoma, for example, being divided into the narrow angle, or obstructed angle, type and the open angle type. At the end of each section is a collection of various medicaments arranged according to their field of action and listed as prescriptions, with directions to the patient for use. It is a handy book to have around the office for quick reference.

An Atlas of Diseases of the Eye. Compiled by E. S. Perkins and Peter Hansell. Price, $10.00. Little, Brown & Company, 34 Beacon St., Boston 6, 1957.

Anyone who has had medical students to teach knows how difficult it is to obtain patients with the commoner inflammatory diseases of the eyes and adnexa at the time of teaching rounds. Few patients with inflammatory lesions of the lids and conjunctiva come to the eye dispensary these days, since the general physician, who sees them first, cures them with antibiotics, and yet these are just the cases that the medical student should be shown and told how to treat.

This beautiful atlas will go a long way toward solving this problem, as the vast majority of diseases depicted are those which the general physician will see. The illustrations, all of them in color, are excellent, and each is accompanied by a short descriptive paragraph. The illustrations of external diseases are largely photographs, while the majority of the fundus lesions pictures are paintings. This is as it should be, since fundus photographs have not yet reached the state of perfection which enables an inexperienced observer to see the details which are of paramount importance. All of these pictures could easily be rephotographed was Kodachrome film and made up into slides for teaching purposes, after permission has been obtained from the authors and the publisher, and they would be a valuable backlog to fill in whenever clinical material is not readily available.

The book is beautifully printed, and the publishers are to be congratulated on doing such a beautiful atlas. A relatively low cost has been made possible by the generosity and public spirit of the firm of Roche Products, Ltd., one of the large English pharmaceutical firms. As Sir Stewart Duke-Elder says in his foreword, "The subsidy of an atlas of this type by Roche Products, Ltd., so that it may become available to the profession at about one tenth of its cost price, is a novel contribution to the dissemination of knowledge. For this, and insofar as the atlas may aid in the treatment of our patient, we are grateful to them."

Children's Eye Problems. By Emanuel Krimsky, M.D. Price, $7.50. Pp. 175. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1956.

The aim of this book is stated "to provide the pediatrician and the general practitioner with a practical, usable guide to the understanding of children's eye problems and, at the same time, to present to the ophthalmologist a plan for dealing with the child as a whole by emphasizing environmental, psychologic, hereditary and systemic influences." This comprehensive and worthy goal is difficult to attain within the space of 175 pages. Apparently in an effort to cover a broad field, the author has given very few specific and practical details which might be of use in the management of children's eye problems.

The techniques for examination of the eye seem inadequate, even for a pediatrician, for example, in recommending ophthalmoscopy at a distance of 1 ft. from the eye to detect the presence or absence of a red reflex. Almost one page is spent on the measurement of the height of papilledema, without any discussion of other features considered by many to be of more importance in the diagnosis of early papilledema. In discussing congenital glaucoma, the author states, "Digital palpation of the eyeball to measure tenseness is often preferred to instrument methods which yield unsatisfactory readings and require extra care lest the cornea become ulcerated from trauma by the instrument."

In diagnosis, considerable space is rightly taken in the discussion of "cross eye," which has been of major interest to the author, and the illustrations are good. Relatively little time is given to uveitis, fundus lesions, and non-neurological conditions affecting the eye, such as juvenile diabetes and febrile illnesses. In

many instances differential diagnosis consists of the listing of many diverse conditions, including highly specialized ophthalmological terms with few helpful descriptions to aid in the differentiation.

The book does not seem to be intended for use in treatment but rather to introduce the pediatrician to ocular disorders in children. Some of the recommendations which are given do not include more recent agents, such as the newer and more specific antibiotics, e. g. (instead of penicillin systemically for Koch-Weeks conjunctivitis), antituberculosis drugs, antitoxoplasmosis drugs, etc. Well-accepted surgical procedures are hardly mentioned for such conditions as ptosis and dacryocystitis of infancy and childhood, and perhaps the author is unduly pessimistic about the outcome of other surgical procedures in children except in the case of convergent strabismus, in discussion of which he states that the parents can be assured "that the operation is harmless, that the eyes will probably be improved, certainly not made worse."

Perhaps the most disturbing thing about this book are numerous statements, to which the reviewer, at least, takes exception, as illustrated in the following quotations: "Possible causes [ptosis or drooping of the upper lid] include: . . . paralysis of the facial nerve"; "massaging the lids with irritating yellow oxide of mercury in strength as high as 1% has been a common practice (for marginal blepharitis)," and instead of this, the author recommends as part of his treatment "careful application of 5% silver nitrate solution to the lid margins," and "use of cortisone eye ointment"; subconjunctival hemorrhages "may also result from malignant hypertension" (presumably in children); following injury to the conjunctiva, "the fear of complicating local infection is remote, especially with the preventive administration of tetanus antitoxin, penicillin injections, and the local use of cortisone"; "microcornea may be a benign anomaly, or may be the forerunner of infantile glaucoma"; "the iris proper consists of a pigment layer in front . . . the muscles of the iris are deftly concealed behind the anterior pigment layer"; "because the reason for this type of cataract [rubellar] is already established, it can no longer be classed as strictly congenital"; in monocular aphakia in children, "it merely means that the eye is a reserve eye which can be made to see at any time an eyeglass is prescribed" (nothing mentioned about amblyopia ex anopsia); concerning the physiology of vision, "in the brief fraction of a second the image is returned [from the brain center] to the eye along the same nerve fibers in the optic nerve and then projected into space as a beautiful colored image of natural size"; included in the treatment of virus infections of the cornea is "prescribing eyedrops which might counteract the offending virus, such as cortisone" and the statement, "penicillin injections are often inert against virus infections"; "a measure often successful for corneal infections is the local instillation of cortisone eyedrops, usually every hour, and continued for a few days. The results are often dramatic and occur within a few days. Failure of cortisone to help the corneal condition often suggests herpes simplex especially when there is also a 'fever blister' on the lips, or suspicious herpetic lesions in the mouth, the gums, the palate, the vagina and other parts of the body"; after perforating injuries of the eye, the danger of sympathetic inflammation is pointed out, and "such intensive treatment includes observance of the same measures as noted under care of virus infections of the cornea" (nothing stated about early enucleation of the injured eye as prophylaxis); "damage to the ocular muscles [superior and inferior obliques] is a frequent hazard on the golf course. Golf ball injuries may also produce rupture of the eyeball or acid burns from the acid fluid contents when the golf ball is shattered"; "treatment is usually inadvisable in congenital cross eye"; in monocular esotropia with amblyopia ex anopsia, "though sight may in rare instances be improved by forcing the child to wear an eye patch, more often the eye reverts to its original state after the patch is removed." "This visual enslavement is a nerve-wracking procedure for both mother and child. It is questionable whether the conditions for successful occlusion of an eye can be carefully observed" (the author recommends atropine occlusion); "injection of hot or cold water into the external auditory meatus . . . nystagmus is observed with the quick component in the direction of the ear that is irrigated."

The author has done well in pointing out the probable lack of value of eye exercises to correct myopia and the undesirability of sharp restriction of the visual activities of a young myope in a vain effort to slow down progression. The section on fusion training in strabismus is well done.

Although the stated aim of this book is excellent, the reviewer feels that it does not attain its objective, that there is insufficient detailed information to be of practical use, and that some of the statements might be misinterpreted by the nonophthalmologist reader.

Physiology of the Ocular and Cerebrospinal Fluids. By Hugh Davson. Price, $14.00. Pp 388, with 109 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1956.

In recent years so much progress has been made in our understanding of aqueous humor formation and composition that many workers in the field as well as students of ophthalmology have felt a need for a textbook covering recent advances and concepts. Dr. Davson has carried out extensive experimental work on this subject over a period of many years and is well qualified for the task of compiling an authoritative review.

The present volume presents a well-written expansion of a series of papers. In a lucid and persuasive fashion, the data, theories, and conclusions of the author are reiterated. Even on some of the most complex aspects of the subject matter, the book reads easily and convincingly. It is particularly unfortunate, therefore, that, as the author admits, "the presentation of the facts has been strongly colored by my own point of view." The exclusion or distortion of important work of others results in a book which fails to fulfill the need for an up-to-date and comprehensive text on this subject matter. Furthermore, the author's stated desire to produce an "introduction" which "lays bare a problem" has not been accomplished.

The first part of the book presents a summary of the pertinent anatomical relationships concerned with the aqueous humor and cerebrospinal fluid. There is very little reference in subsequent chapters to this information. The second section is concerned with the composition of the aqueous humor and cerebrospinal fluid and speculation as to mechanisms of their formation. Last, there is a discussion of considerations of pressures in the eye and cerebrospinal system.

The author has obviously spent much time and effort in compiling a long bibliography. Although this bibliography is a valuable contribution as a reference source, it would have proved of much greater usefulness if it also contained the many references to significant contributions in conflict with the views of the author.

The author's mathematical formulation for aqueous humor dynamic is repeated and expanded, with no mention made of criticisms of it by others. Supposition as to the composition of the posterior chamber aqueous humor is used without reference to the available results of detailed posterior chamber analyses. The important theoretical considerations of Friedenwald and Kinsey are disregarded without mention or are relegated to such footnotes as "I have too little sympathy for the highly speculative reasoning displayed by this author."

The casual reader will have great difficulty in distinguishing between facts derived from the basic work of others and the contributions and speculations of Dr. Davson. As one misguided student who accepted the views presented in this book commented, "the opposition of so many prominent workers in the field must have made it most difficult for Davson to convince ophthalmologists that the aqueous humor was a secretory product!" The gross inaccuracy of this impression was readily revealed by reference to suitable literature. The numerous footnotes are perhaps an attempt to correct or rationalize the serious omissions. Unfortunately, they serve to bury some important contributions in small print or to present unnecessary personal attacks on other workers. For example, in spite of current thinking and usage in anesthesiology, the author states, concerning the experimental use of curare in animals, "such brutality, however, is forbidden by law in the present author's country, and even if it were not, I trust that common decency would prevent it."

To the informed worker in this field, this book has little to offer except as a summary of Davson's data and views. It should have little appeal to the ophthalmologist from a clinical point of view. However, the text may be of limited value to the student in the basic sciences of ophthalmology, provided that its inadequacies are appreciated and amplified by the instructor. One must emphasize that this is not an "exhaustive review" of the history or an adequate evaluation of the present status of the subject. Perhaps the deficiencies of the book will serve as a stimulus for the production of a much-needed text which adequately deals with the available facts and current concepts of the physiology of the ocular fluids.

Current Therapy 1957. Edited by Howard Conn, M.D. Price, $11.00. Pp. 731. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1957.

This is the ninth volume in the series issued each year covering the recent developments in therapy in general medicine. The only section dealing with opthalmology specifically is on neuritis, optic and retrobulbar, by Max Fein. The book continues to be a useful review of current treatment.

Transactions of the Pacific Coast Oto-Ophthalmological Society, Vol. 37. Price, not given. Pp. 396. Dr. C. Allen Dickey, 450 Sutter St., San Francisco, 1956.

The 40th Annual Meeting of the Pacific Coast Oto-Ophthalmological Society was held in Phoenix, Ariz., April 15 to 19, 1956. The following papers were presented dealing with ophthalmology:

Epiphora: Its Relation to the Anatomic Structures and Surgery of the Medial Canthal Region (President's Address)
Lester T. Jones, M.D.

Differential Diagnosis and Management of Lesions Involving the Orbit
Albert C. Furstenberg, M.D.

Keratocanthoma of the Eyelid
H. R. Crisman, M.D., and Leonard Christensen, M.D.

Experimental Scleral Surgery of the Monkey
Taylor Asbury, M.D., and Daniel G. Vaughan, M.D.

Marcus Gunn Phenomenon Following Squint and Ptosis Surgery
Derek G. Simpson, M.D.

A Modification of the Friedenwald-Guyton Ptosis Operation
J. W. Bettman, M.D.

New Orthoptic Techniques
Frances Fowler

Miliary Retinal Aneurysms
Robert L. Tour, M.D.

Orbital Metastasis of Renal Carcinoma
C. E. Van Arnam, M.D., and Max Fine, M.D.

The Differential Diagnosis of Superficial Keratitis
Phillips Thygeson, M.D., and Samuel J. Kimura, M.D.

Vascular Lesions Affecting the Visual Pathways
Harold B. Alexander, M.D.

Some Basic Considerations in the Management of Lid Injuries
Milton Singer, M.D.

Anesthesia for the Pediatric Patient
J. D. Stringham, M.D.

Encyclopedia medico-chirurgicale. Edited by E. Velter and G. Renard. Price, not given. Encyclopedia medico-chirurgicale, 18, Rue Seguier, Paris 6e, 1956.

These two massive tones on ophthalmology measure twelve by thirteen inches and contain a resume of all of ophthalmology in French by numerous French authors, collaborating with the editors. While the material they contain is well selected and beautifully illustrated, the size and weight of the books makes them so impractical as to be almost worthless. In addition, they are not bound, but

the loose pages are held in place by a spring mechanism which is not very secure. It is evident that the publication of advances in ophthalmology is intended, which can be slipped into the proper places for reference. The unwieldiness of these volumes makes them a vertitable white elephant in any library, since no ordinary shelves will accommodate them.

Modern Problems of Ophthalmology. Edited by E. B. Streiff and J. Babel. Price, Fr. 60. Pp. 740, with 220 illustrations and 11 plates (4 in color). S. Karger A. G., Arnold Böcklinstrasse 25, Basel, 1957.

This volume is presented in honor of Professor Franceschetti on the occasion of his 60th birthday, and consists of an excellent collection of papers from well-known authors all over the world. The contents are as follows:

Introduction
E. B. Streiff

Ultrastructures
C. A. Baud

Cornea
G. von Bahr; J. Babel

Aqueous Humor, Capillary Circulation
S. Duke-Elder; M. Amsler; A. Fritz

Vitreous Body, Lens
C. L. Schepens; J. Nordmann; H. K. Muller; O. Kleifeld; U. Dardenne; R. Fuchs; O. Hockwin

Gonioscopy, Glaucoma
H. Goldmann; J. Bock; J. Stepanik; A. Busacca; G. Gordin; J. Malbran

Vascularization of Optical Tract
J. François; A. Neetens; J. M. Collette

Physiology of Vision
G. Wald; E. N. Willmer; F. A. Hamburger; A. Dubois-Poulsen; C. Magis; C. Berens

Electrophysiology
G. Schubert; H. E. Henkes; M. Monnier

Bacteriology, Virology, Tuberculosis, BCG-Vaccination
P. Thygeson; J. de Ruyter; A. C. Woods; S. R. Andersen; E. Frandsen

Allergy, Collagen Disease
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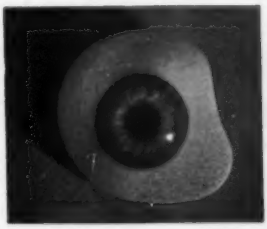

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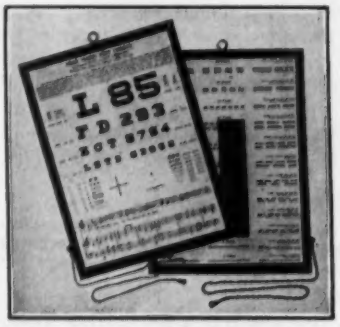

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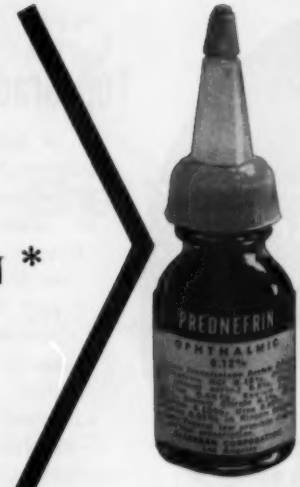

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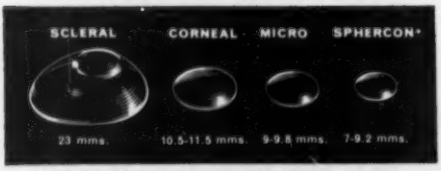

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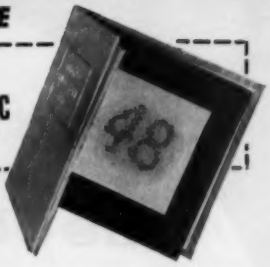

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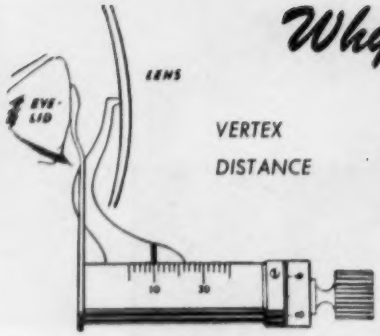

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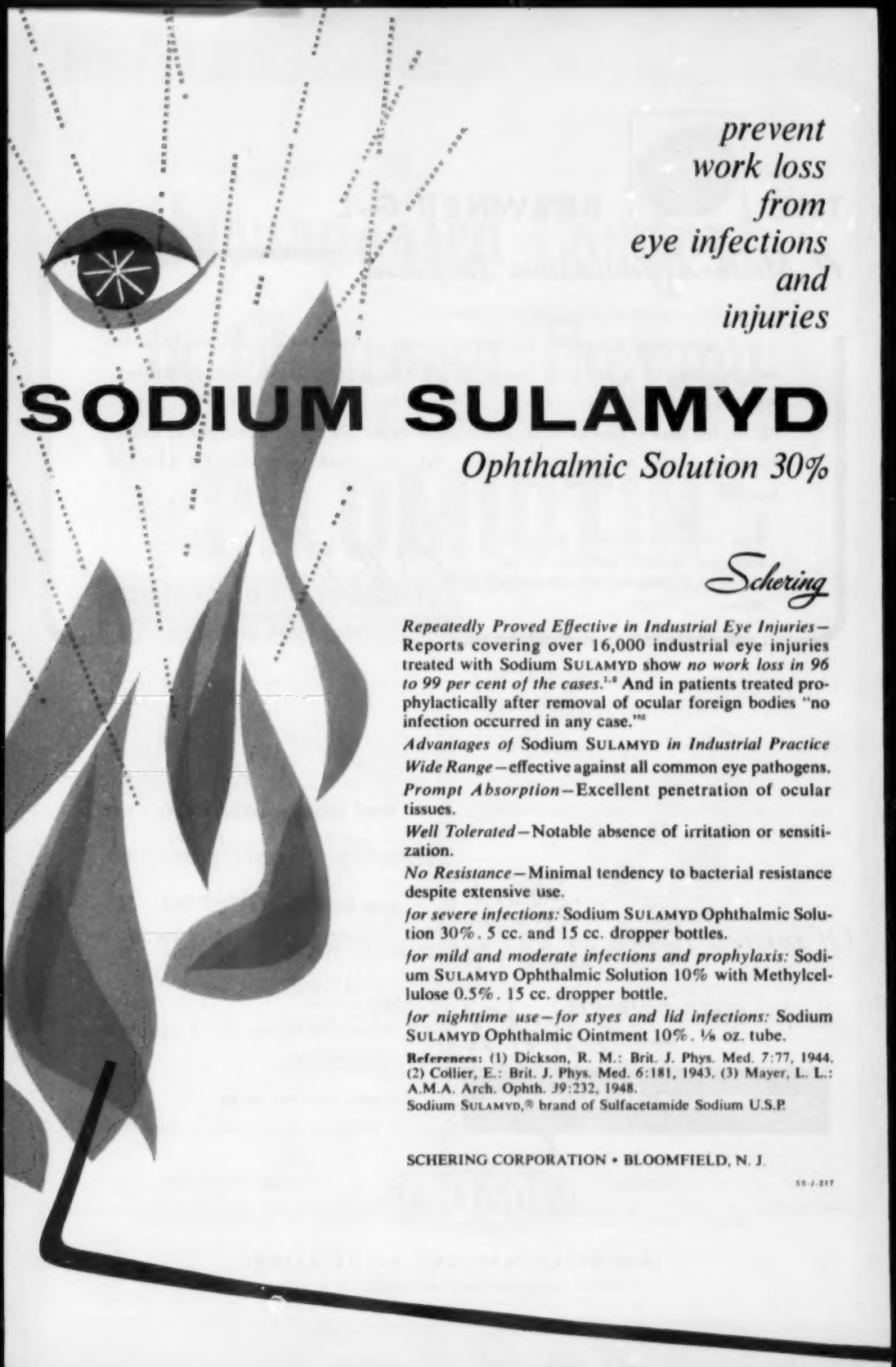

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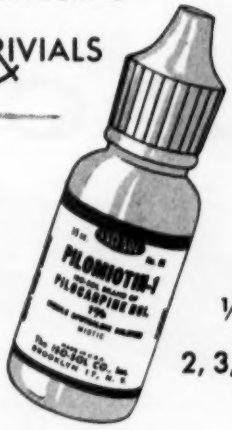

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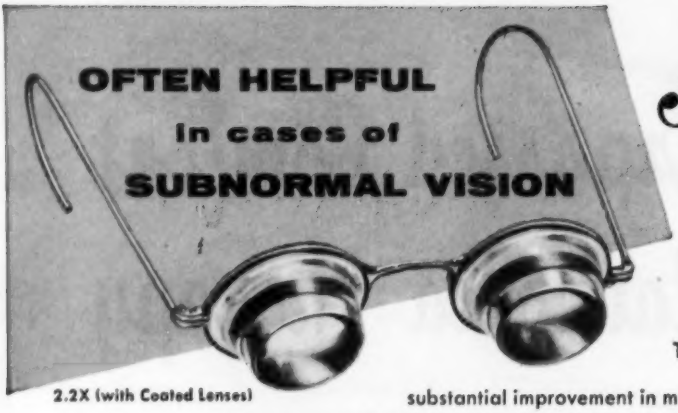

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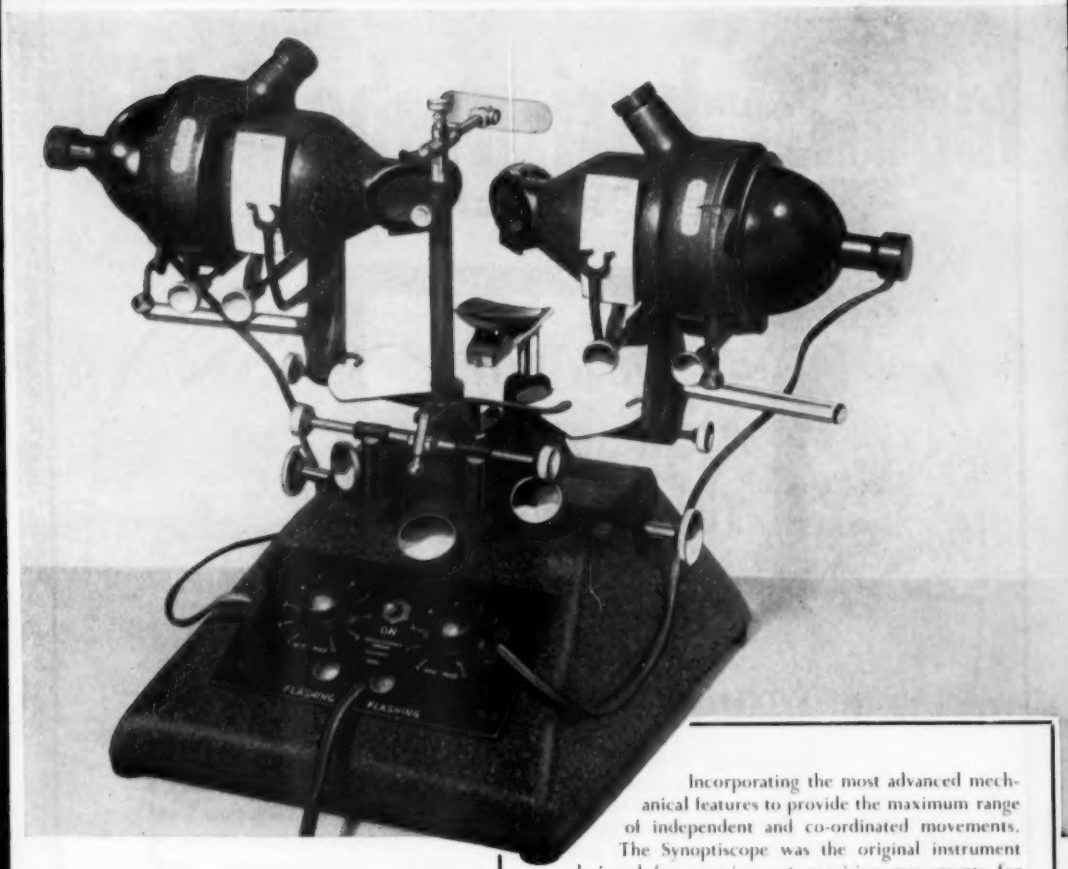

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The patient, a female 68 years of age, was first seen on January 8, 1953, and a diagnosis of right senile cataract was made. The left eye was painful and blind. One week later, an alcohol injection about the left ciliary ganglion relieved the patient of pain and enabled her to retain the eye, which was psychologically most desirable.

On May 18, 1954, a right intracapsular lens extraction was performed without complication. The post-operative course was uneventful and the patient was discharged from the hospital on May 27th. While the patient was still in the hospital, a +10.00D temporary single-vision* lens was ordered and fitted on the patient's first office visit on May 28th. With this lens, the right vision = 20/50.

6-9-54: Manifest O.D. +11.00Dsph. ○ +2.50Dcyl. ax 10 = 20/30—. Rx Right: this in CATAREX T (temporary style) straight-top bifocal. Left: lens to balance. The patient was allowed to retain the previous lens until the new CATAREX T bifocal was received. This plan was followed on all subsequent changes.

7-8-54: Manifest O.D. +11.50Dsph. ○ +1.50Dcyl. ax 15 = 20/25+. Rx Right: this in CATAREX T. Left: lens to balance.

9-9-54: Manifest O.D. +12.00Dsph. ○ +1.25Dcyl. ax 15 = 20/15. Rx Right: this in CATAREX D permanent bifocal. Left: lens to balance.

1-25-56: Sixteen months after securing the permanent CATAREX D bifocal, the Right vision with this lens = 20/15.

This patient, who secured her first CATAREX T (temporary style) lens ten days after cataract surgery and had three different changes, secured her first and only permanent lens approximately four months after surgery. To date, she has not had to have it changed or re-surfaced.

**Single-vision CATAREX T.*

CATAREX 'T' TEMPORARY CATARACT BIFOCAL LENSES BY **VISION-EASE**

Manufacturers of a complete line of quality multifocals

storz
Surgical Instruments

E-6677

The entire magnet, with rectifier built in base, is mounted on ball bearing rubber casters.

Eye Magnet

SCHUMANN

E-6677 Giant Type. The Special conical shaped coil used in this magnet produces the highest magnetic field force, attractive power and penetration. An additional advantage of this conical design is the resulting external form which permits an unobstructed view of the surgical field.

The magnet can be maneuvered toward the surgical field from any angle.

Exact and minute movement of the magnet during the operation is accomplished by a precision hand wheel control. $2600.00

SPECIFICATIONS:

Ball jump height (4mm steel ball), 110mm.
Penetration: at a distance of 30mm, F = 60-70.
Dimensions: Heights 6', base diameter, 2'.
Weight: 324 lbs.
Electrical Requirement: 220 Volts, 45 amp. Alternating current.

Storz Instrument Company
4570 Audubon Avenue
St. Louis, Missouri

"The Best Is Yet to Come..."

E. H. Titmus, Jr.

A PROGRESS REPORT
from
E. H. TITMUS, JR.
President
TITMUS OPTICAL COMPANY, INC.

Although eyewear prescriptions increased more than 250% during the last decade, more than 40% of the adult and school population are sub-standard in visual performance desirable for school and job achievement, according to reliable estimates.

In this fact lies a challenge to the optical industry. As a manufacturer, Titmus Optical Company is meeting this challenge through a progressive development program in vision instrumentation and techniques, new concepts in lens, frame and sun wear design, and marketing policies designed to best serve the practitioner and his patients. In this brief report I would like to touch on some of these developments.

Division of Applied Visual Science Formed

This Division, headed by Dr. Richard Feinberg, is concerned with the development of ophthalmic instruments and their applications, and includes a Research and Information Department. It also encompasses a Department of Occupational Vision under R. A. Sherman, concerned with school, motor vehicle driver, and industrial vision. A new concept in vision instrumentation and techniques, now perfected by this Division, will be announced soon.

T/O "Normalsite" Lens Minimizes Marginal Astigmatism

The "Normalsite" single vision lens, developed by Titmus, has introduced a new concept in lens design. The Titmus "Normalsite" lens minimizes marginal astigmatism, producing marginal images of equal sharpness at both near and far, and offering comfortable vision over the entire visual range.

"Professional Only" is T/O Marketing Policy

Titmus Optical Company has taken a leading part in the industry's effort to preserve conventional profession-patient relationships, and we invite others to join with us. To this end Titmus products are available only through professional optical channels. Because of this Titmus policy the profession may provide ophthalmic materials and services meeting the most exacting standards of quality . . . without the stigma of market-place competition.

Independent Supplier, "Golden Link to Complete Service"

Only the independent supplier can provide the "cream" of the market from *many* manufacturers through *one* source.

Early this year T/O initiated a program to dramatize this basic service, symbolized by the "Golden Link" insignia reproduced at the bottom of this page. This program met with instant and enthusiastic response from the profession and suppliers alike . . . another step in T/O's continuing effort to serve the best interests of the optical profession.

☆ ☆ ☆

In this brief report it has been possible only to touch on some of the steps we are taking here at Titmus Optical Company to meet the challenge of providing better eye care to the large segment of our population who need it . . . and some of the reasons we feel that, in this never-ending search for improved ophthalmic materials and techniques, "The best is yet to come."

"The Golden Link to Complete Service"